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Development of a Methodology for the Direct Activation of Alcohols Using Cobalt Photocatalysis

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The co-author David B. C. Martin listed in these publications directed and supervised the research which forms the basis for this dissertation. All other co-authors listed in these publications contributed technical expertise.

ABSTRACT OF THE DISSERTATION

Development of a Methodology for the Direct Activation of Alcohols Using Cobalt Photocatalysis
by

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Dr. David B. C. Martin, Chairperson

The utilization of light energy to drive reactions using precious metal catalysts has allowed significant progress in our ability to design new chemical reactions. It remains an ongoing challenge to reduce costs and waste formation by designing catalytic processes with earth-abundant metals, using simple non-toxic substrates and reagents, and generating only benign by-products. The development of new light-driven catalytic reactions to convert simple alcohol-containing chemicals into various functionalized products would be highly valuable. Using a novel cobalt-based radical pathway, we explored the use of cheap, abundant feedstocks to make valuable products while providing new insights into the mechanism of this important type of light-driven catalysis.

This work explores the development of a cobalt-based catalyst system that harnesses light energy to perform the direct functionalization of alcohols via acyl and alkyl radical intermediates. Current methods typically require a pre-activation step, which produces undesirable, often toxic byproducts. The use of abundant cobalt catalysts inspired

by the biochemistry of Vitamin B_{12} provides an alternative mechanism for *in-situ* activation which produces versatile radical intermediates that can participate in a wide variety of chemical transformations including catalytic deoxygenation, radical cyclizations and intermolecular cross-coupling. Stoichiometric pathways were studied for the proposed catalytic system to investigate these Co(II) and Co(III) complexes and the radical intermediates formed under photochemical conditions. A series of alkoxycarbonyl cobalt(III) complexes were prepared by carbonylation of aliphatic alcohols using protocols developed with three distinct ligand systems. Characterization provided structural details for the alkoxycarbonyl complexes previously unknown or uncharacterized. Homolysis-decarboxylation processes demonstrated cleavage of C–O bonds and trapping of the resulting alkyl radicals oxidatively or reductively. Homolysis-lactonization reactions established a method for cyclizations via the acyl radical intermediates, and subsequent application for the synthesis of the limonoid natural product fraxinellonone was investigated. Finally, development of these stoichiometric reactions into a catalytic methodology was explored.

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Chapter 1 : Introduction

1.1 Background

Alcohols are one of the most abundant classes of organic molecules, with the hydroxyl group being prevalent in naturally occurring feedstocks such as sugars and complex natural products. Alcohols are also valuable synthetic intermediates, being readily introduced and converted to a myriad of other functional groups. Most transformations, however, require pre-activation of the hydroxyl group due to the relatively inert nature of the C–OH bond.[1] In particular, radical chemistry relies on conversion to a halide or xanthate ester as a means to overcome the strong C–O bond, which can be weakened by the formation of an adjacent radical (Figure 1.1, A).[2] Transformations such as the Barton–McCombie deoxygenation facilitate cleavage of the strong C–O bond through the reaction of a xanthate ester **1.2** with a tin radical species following this mechanistic pathway (Figure 1.1, B).[3] Radical **1.1** has been further utilized in a variety of fashions, such as simple deoxygenation or complexity-generating C–C bond formation.[3–5] These reactions take advantage of the formation of strong Sn–S bonds, driving the cleavage of a strong C–O bond to form radical **1.1** and ultimate reduction to product **1.3**. Although these methods are extremely useful, the major drawbacks are the requirement of a separate pre-activation step and the generation of stoichiometric waste in both steps of the process, requiring additional purification and disposal of by-products, most commonly containing tin, sulfur and selenium. More recent approaches take advantage of related thiocarbonyl derivatives with iridium photocatalysis to generate a radical or radical anion intermediate with a weakened

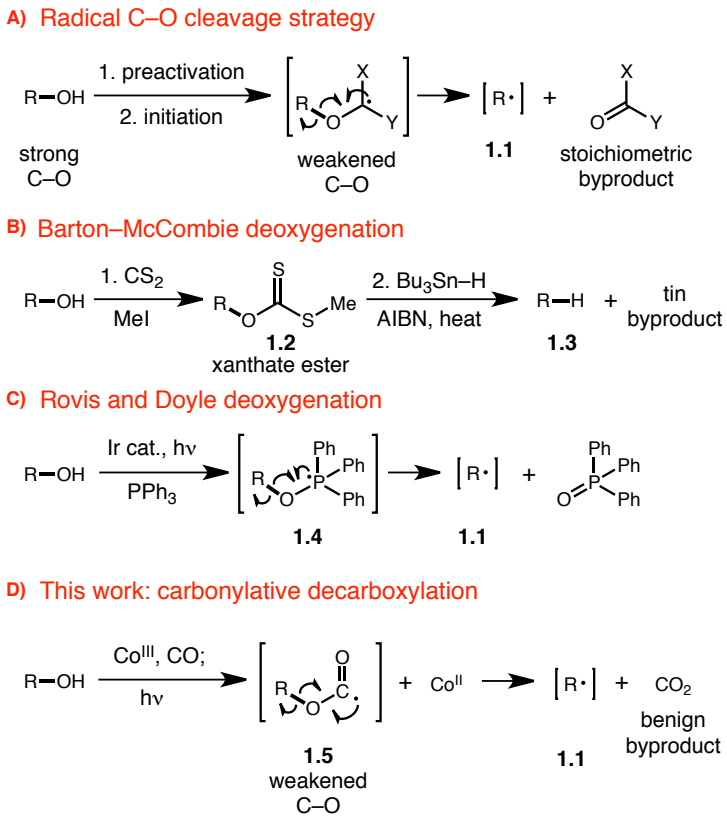


Figure 1.1 Strategies for C–O bond activation of alcohols utilizing cobalt complexes

C–O bond that readily fragments.[6] In 2018, Rovis, Doyle and coworkers reported a unique direct deoxygenation via C–O homolysis with phosphoranyl radicals generated from a phosphine reagent and Ir photocatalyst (Figure 1.1, C).[7] This fascinating method represents a creative advance in the field of alcohol activation, however it was limited to 1º benzylic alcohols and carboxylic acids. With the goal of developing a system that avoids stoichiometric preactivation and generates benign, low molecular weight by-products, we sought a method for direct activation using an earth abundant metal catalyst. Generation of acyl radical **1.5** from a cobalt photocatalyst and carbon monoxide (Figure 1.1, D) would exhibit the same weakened C–O bond as xanthate ester **1.2** and phosphoranyl radical **1.4**. Decarboxylation would produce the desired radical **1.1** where numerous productive

reactions could proceed. Rendering this method catalytic would represent a very valuable advance in the efficient use of alcohols in radical chemistry.

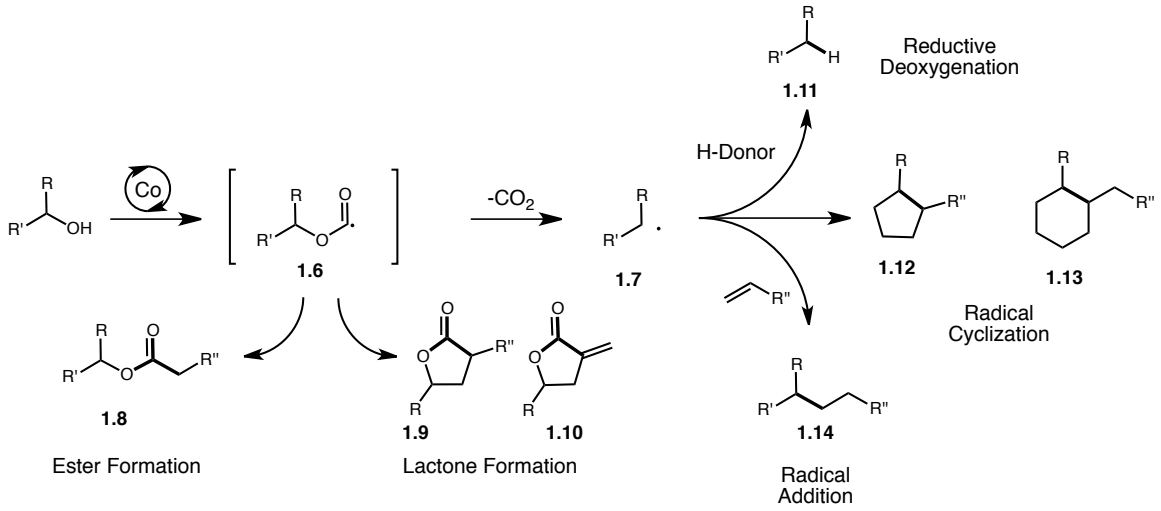


Figure 1.2 Highly versatile applications of our method for the direct activation of alcohols

This improved method would allow the direct conversion of alcohols into an activated species, with overall generation of only water, CO_2 or similarly benign byproducts. This strategy could be achieved by a metal-catalyzed formation of acyl radical **1.6** which provides access to ester product **1.8** or lactones **1.9** and **1.10** (Figure 1.2). The decarboxylation of acyl radical **1.6** to alkyl radical **1.7** provides access to an even larger variety of possible products. Radical cyclization provides products **1.12** and **1.13** and radical cross-coupling would yield product **1.14**. Finally, similar to Barton-McCombie chemistry, reduction of decarboxylated radical **1.7** provides the deoxygenation product **1.11**. This strategy provides a conceptually novel way of accessing a variety of radical intermediates that have proven versatility in organic synthesis. In addition, the reduction of waste byproducts would render these reaction types amenable to large-scale applications that are generally not practical using traditional activation methods.

1.2 Model Systems

In order to develop a methodology for this direct activation of alcohols an appropriate catalyst must be established that will carbonylate and generate our desired

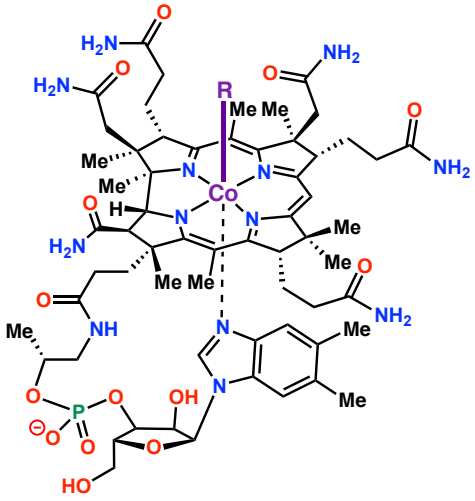
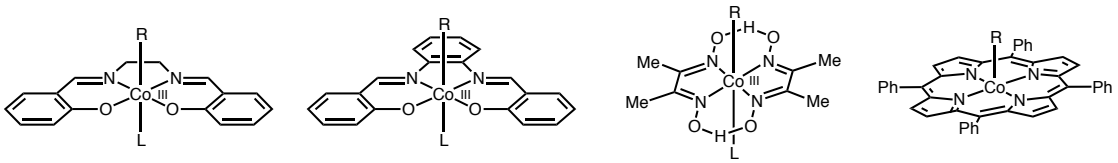


Figure 1.4 Vitamin B_{12}

radical when irradiated. For this, one may look to Nature for inspiration; coenzymes B_{12} (Figure 1.4) have been extensively studied for their ability to undergo reversible Co–C bond cleavage to generate carbon-centered radicals in numerous important enzymatic processes.[8] Due to the complexity of these coenzymes, many model systems have been developed to mimic this homolytic bond cleavage that are more synthetically available, such as cobalt complexes with salen, salophen and dimethylgyloxime ligands (Figure 1.3).[9]



cobalt-salen
Co(salen)LR

cobalt-salophen
Co(salph)LR

cobaloxime
Co(dmgH)$_2$LR

cobalt-porphyrin
Co(porph)R

(L = py, benzimidazole, PPh_3, H_2O, etc)

Figure 1.3 Cobalt complexes as models for vitamin B_{12}

Alkyl-cobalt derivatives of these complexes are known to generate radicals via homolysis initiated by light or heat due to their weak Co–C bonds.[10] Many methods to generate these alkyl-cobalt species have been reported, as outlined with the following examples.

1.3 Alkyl Cobaloxime Complexes

Hydrocobaltation is the addition of Co–H across alkenes and was originally investigated by Schrauzer and coworkers in 1966.[11] Pattenden and coworkers expanded this principle of hydrocobaltation and dehydrocobaltation to cross couple sp^2 carbons and form functionalized alkenes.[12,13] This phenomenon was found to be regioselective and pH dependent (Figure 1.5). Hydrocobaltation of alkenes with cobaloxime dimer and hydrogen give the alkylcobaloxime. Selectivity for complex **1.15** was observed under basic conditions and complex **1.16** is favored by neutral conditions. Schrauzer and coworkers proposed that under basic conditions a Co(I) anion is formed and reacted via standard nucleophilic addition to an olefin to give regioselective product **1.15**.[11] Irradiation of isolated alkylcobaloxime **1.15** or **1.16** initiates Co-C bond cleavage producing an alkyl radical which rapidly reacts with an alkene acceptor. Recombination with the cobaloxime

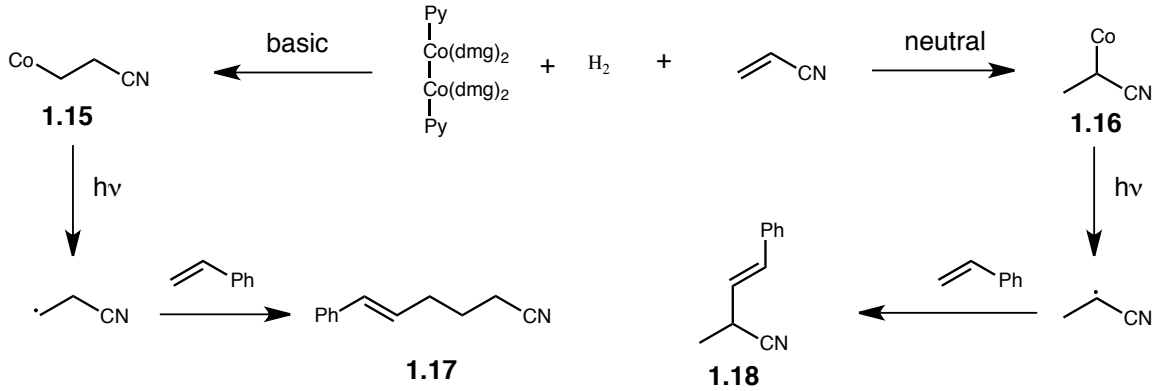


Figure 1.5 Hydrocobaltation with cobaloximes leading to sp^2 cross coupling

and subsequent dehydrocobaltation gave the new alkene products **1.17** and **1.18**. These methods were later improved upon by Carreira and coworkers when they developed a cobalt-catalyzed Heck-type cyclization using the precedent from Costa and coworkers. [14]

1.4 Alkyl and Acyl Salen and Salophen Complexes

Pattenden and coworkers have extensively studied alkyl and acyl-organocobalt species. The preparation of alkyl cobalt species is achieved via the reduction of Co(II) species with Na/Hg amalgam to Co(I) and treatment with an alkyl halide.[15] These alkyl-cobalt complexes have been utilized for radical cyclizations[16,17] and initiation of living radical for polymerizations.[18,19] Interestingly, these Co(I) species were able to undergo single electron transfer which facilitated radical cyclization of the aryl iodide precursor to a hydrobenzofuran methyl radical (Figure 1.6). The cyclized product then recombined with the Co(II) radical to form an alkyl cobalt(III) product **1.19**.[20] When these alkyl complexes were subjected to light (100 W Hg lamp or 300W sun lamp) in the presence of oxygen, the

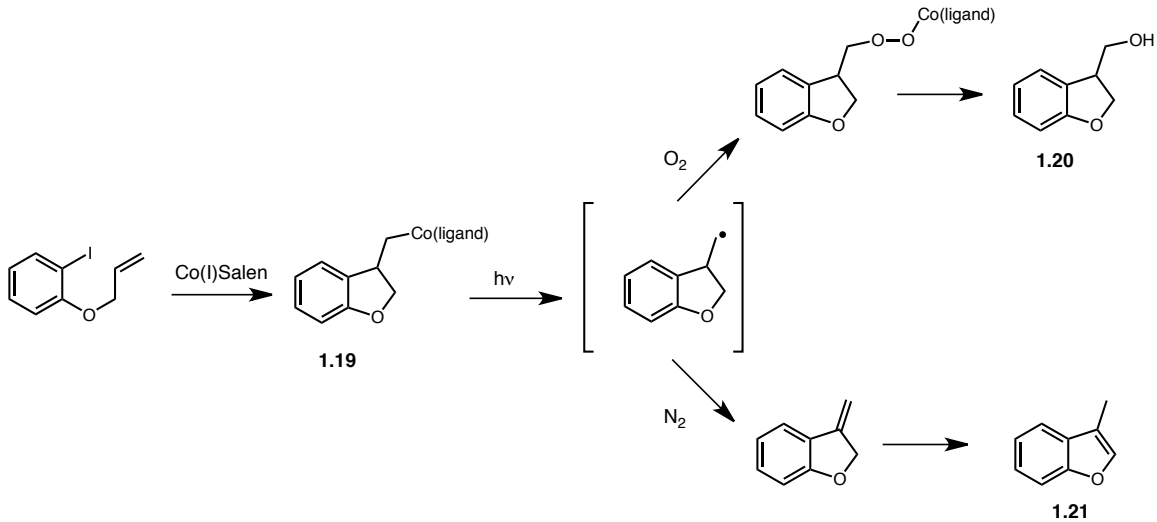


Figure 1.6 Cobalt-mediated radical cyclization

unstable peroxide complex was formed and upon reduction produced the alcohol product **1.20**.[10] The same reaction run under a nitrogen atmosphere produced 3-methylbenzofuran **1.21**, due to β-hydride elimination and isomerization. Pattenden demonstrated this cyclization with cobalt salen and later a cobalt salophen-py complex;[21] however, cobaloxime and cobalamin Co(I) derivatives did not undergo this cyclization presumably due to the reduced nucleophilicity.[22] To confirm the radical intermediate, irradiation of complex **1.19** in the presence of TEMPO was performed and the trapped product **1.22** was observed (Figure 1.7).[23]

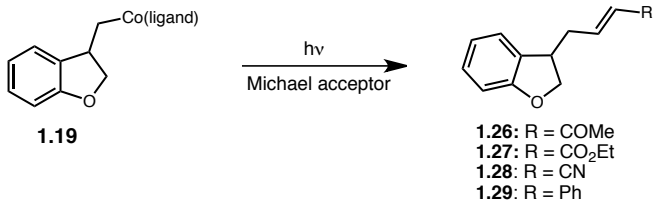


Figure 1.7 Irradiation of **1.19** to give a variety of products a) TEMPO, 50% yield b) PhSSPh, 72% yield or PhSeSePh, 55% yield c) NO, 73% yield d) SO_2, 20% yield

Radical additions were also tested with disulfides and diselenides to achieve the corresponding sulfide or selenide product **1.23**. Additionally, irradiation in the presence of nitrogen monoxide or sulfur dioxide gave the oxime **1.24** (and upon reduction the corresponding amine) or the sulphinic acid **1.25**, respectively. These radicals generated by the homolysis of the Co–C bond were also tested for their ability to do Giese reactions

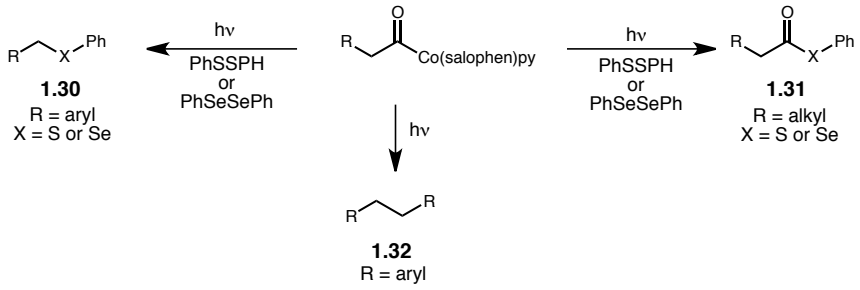


Figure 1.8 Giese reactions from irradiation of **1.19**

(Figure 1.8).[24] Numerous alkene acceptors were tested, and the β-hydrogen eliminated products **1.26**–**1.29** were observed. Minimal isolated yields were reported for Giese products **1.26**–**1.28** (~5% yield), although when styrene was employed as an alkene acceptor a drastic increase in yield was observed (72% yield). Irradiation reactions with alkyl cobalt species gives insight into the behavior of these model complexes under photolytic conditions.

In addition to alkyl complexes, Pattenden and coworkers also synthesized some acyl cobalt salophen complexes and observed similar reactivity in radical cyclization[25] and additions into Michael acceptors.[26,27] These acyl complexes were also studied for their addition into disulfides and diselenides and behaved similarly to their alkyl counterparts, forming the corresponding thioethers and selenoesters **1.31** (Figure 1.9). Interestingly, when the R group was an alkyl group, the acyl radical added directly into the disulfide/diselenide; however, when an aryl R group was employed decarbonylated product **1.30** was observed. Similarly, reaction with radical trapping agents such as TEMPO and aryl R groups exhibited this same trend.[27] Pattenden and coworkers referred to this as a 'cobalt-Hunsdiecker'. It was noted that if decarbonylation leads to a benzylic

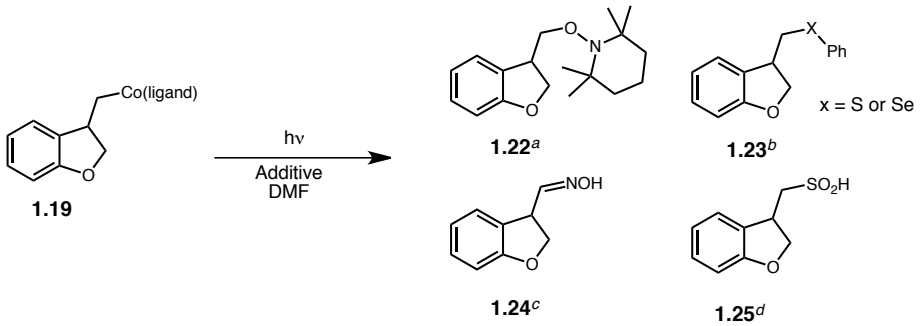


Figure 1.9 Irradiation of acyl complexes with and without disulfides and diselenides

or α-aryl radical, decarbonylation was observed before radical trapping. They reported attempts to expand this 'cobalt-Hunsdiecker' method to non-aryl substituents, but even a *tert*-butyl substrate was unsuccessful. Additionally, if reactions were run in the absence of radical trapping agents the decarbonylated diarylethane **1.32** was observed. Direct dimerization of the acyl radical to form a 1,2-dione was never observed.[28]

1.5 Alkoxycarbonyl Salen and Salophen Complexes

Costa and coworkers[17] developed a method to synthesize these alkoxycarbonyl compounds by initially treating a Co(II) complex **1.34** or Co(III) complex **1.33** with Na/Hg amalgam to generate Co(I) species **1.35**.[3–7] Treatment of **1.35** with acyl chlorides or anhydrides results in alkoxycarbonyl complexes of this type **1.36** (Figure 1.10, Route A). This method's use of strong reductants such as Na/Hg amalgam and the necessity of highly reactive chloroformate reagents significantly limits the scope and utility. Conversely, limited examples of a direct path using a carbonylation reaction and simple alcohols were reported by Costa and coworkers (Figure 1.10, Route B),[29] a process that has been significantly expanded and improved upon by our research efforts.

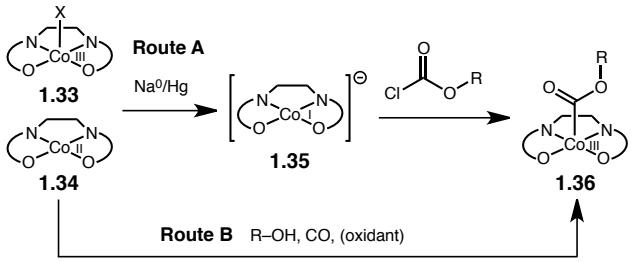


Figure 1.10 Routes to alkoxycarbonyl complex **1.36**

1.6 Proposed Catalytic Cycle

The proposed strategy for alcohol activation builds upon several known, distinct reactions that are each well established for the specific cobalt model complexes under investigation. Using radical deoxygenation as a representative transformation, the overall mechanism of the process is presented in Figure 1.11 and involves the fundamental steps of (A) carbonylation to generate an alkoxycarbonyl complex **1.37**, (B) light-initiated Co–C bond homolysis to produce acyl radical **1.38** and a cobalt(II) species, and (C) decarboxylation to generate the corresponding alkyl radical **1.39**. Hydrogen atom transfer (HAT) (D) produces the desired reduced product **1.40**. Turnover step E provides the final alkyl product and reoxidizes cobalt to return the cobalt(III) catalyst. The overall process is redox neutral, with CO serving as the reducing agent and CO_2 as the only stoichiometric by-product. Due to the relative stability of organometallic cobalt(III) complexes, each step

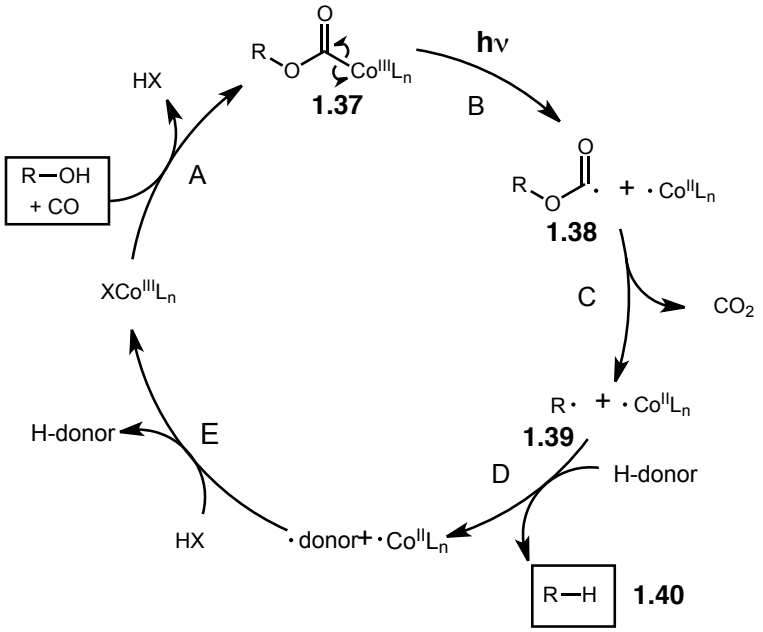
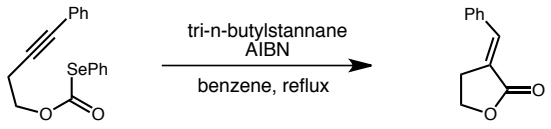


Figure 1.11 Proposed mechanism for cobalt-catalyzed alcohol activation

of the catalytic process is being studied through stoichiometric experiments to construct a synthetic cycle. This approach allows a more detailed understanding of the substrate and ligand effects on each step of the cycle, facilitating catalytic investigations.

1.7 Generation of Alkoxycarbonyl Radicals

The proposed method for the generation of alkoxycarbonyl radicals, discussed above would provide a novel strategy for the formation of these valuable radical species. Previously, alkoxycarbonyl radicals have been formed either from alkoxycarbonyl chlorides or selenides or N-phthalimidoyl oxalates. Bach and coworkers developed a method to preform lactonizations using alkoxycarbonyl radicals generated from acyl selenides, in which acyl selenide **1.41** in the presence of AIBN and tri-n-butylstannane in refluxing benzene can produce lactone **1.42** in 87% yield.[30] Boger and coworkers expanded the utility of these radicals in macrocycle formations with intramolecular Giese additions.[31] These reactions demonstrate the utility of alkoxycarbonyl radicals in synthesis; however, they require the formation of these highly reactive intermediates and harsh reaction conditions.



1.41 **1.42**

Figure 1.12 Lactonization from alkoxycarbonyl radical

More recently, Overman and coworkers developed a method for generating alkoxycarbonyl radicals via N-phthalimidoyl oxalates for use in radical conjugate additions.[32,33] In this system, an alcohol is pre-activated with N-phthalimidoyl

chlorooxalate to form compound **1.43** (Figure 1.13). Using a ruthenium or iridium photocatalyst to initiate single electron transfer (SET) and radical fragmentation pathways,

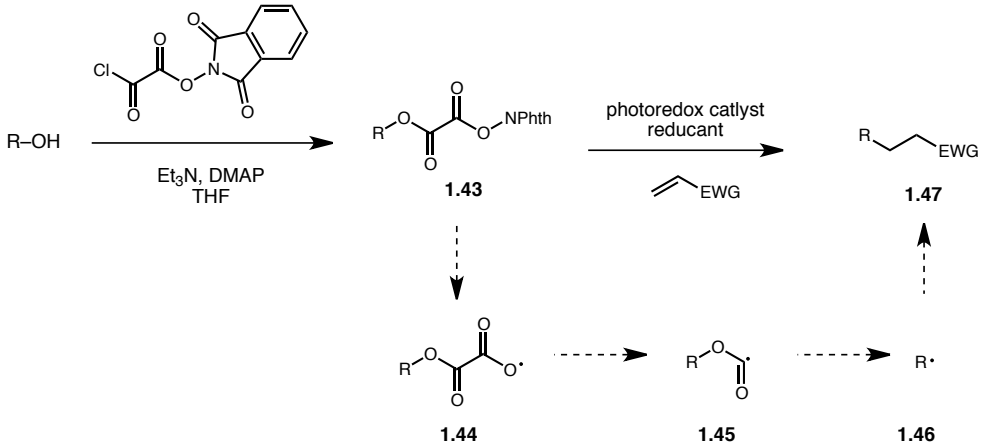


Figure 1.13 Alkoxycarbonyl radicals formed from N-phthalimidoyl oxalate

recently popularized by MacMillan and coworkers,[34] the carboxyl radical **1.44** is formed and rapidly decarboxylates to the alkoxycarbonyl radical **1.45**. In this work, radical **1.45** decarboxylates again to give alkyl radical **1.46** and ultimately a conjugate addition into an electron deficient alkene forms product **1.47**. This method of pre-activation-double decarboxylation demonstrates an avenue to these versatile alkyl radicals.

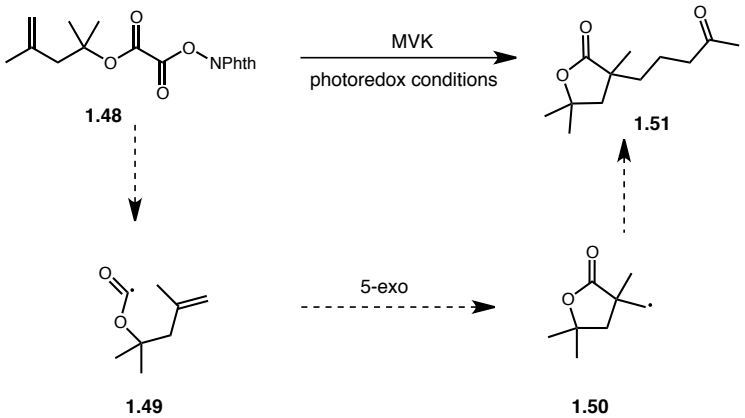


Figure 1.14 Lactonization of alkoxycarbonyl radical **1.49**

Interestingly, the rate of the alkoxycarbonyl radical decarboxylation is significantly slower than that of carboxyl radicals.[35,36] Overman and coworkers observed this when

radical trapping occurred before the second decarboxylation. As shown in Figure 1.14, this rate difference was demonstrated when the rate of 5-*exo* cyclization of alkoxycarbonyl radical **1.49** was faster than the second decarboxylation, resulting in lactone radical **1.50**.[37,38] Conjugate radical addition into methyl vinyl ketone (MVK) produced the lactone product **1.51**. This slow decarboxylation of radical **1.49** is unsurprising based on previous kinetic studies.[36]

1.8 Decarboxylation Rates of Alkoxycarbonyl Radicals

Newcomb and coworkers have reported kinetic studies of these radicals using laser flash photolysis (Figure 1.15).[39] Irradiation of PTOC oxalate **1.52** with 355 nm light in a flow cell promotes homolysis of the N–O bond to give carboxyl radical **1.53**. Decarboxylation of radical **1.53** is fast and results in alkoxycarbonyl radical **1.54**. The slow decarboxylation of **1.54** to alkyl radical **1.55** and fast ring opening to benzylic radical **1.56** was measured by time resolved UV spectra based on the introduction of the UV active benzylic radical **1.56**. The rates determined in these reactions, 0.7–1.4 x 10^8 $M^{-1}s^{-1}$, are

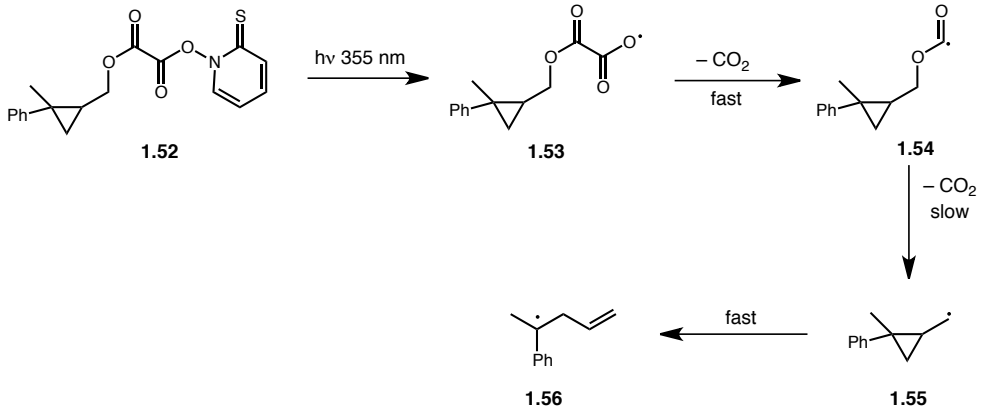


Figure 1.15 Kinetic studies for rate of decarboxylation of alkoxycarbonyl radicals

consistent with work by Beckwith and coworkers who determined that decarboxylation resulting in benzylic radicals is 60 times faster than decarboxylation to form a *tert*-butyl radical.[36,40] When decarboxylation is slow, other radical reactions are observed such as cyclization, hydrogen atom transfer, or trapping with nitroxyl radicals. These principles were used in the development of our catalytic methods and choice of alcohol precursors.

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Chapter 2 : Synthesis of Alkoxycarbonyl Cobalt Salophen Complexes

2.1 Introduction

Since the structural elucidation of cobalamin, alkyl cobalt complexes have been extensively studied due to their importance in both biochemical investigations and catalytic transformations.[1–4] Cobalt salophen complexes are a commonly studied motif due to their ease of synthesis and stability to air and water.[5,6] The Co–C bond strengths of alkyl salophen complexes have been determined through detailed studies by Halpern and others, and were found to be similar to analogous vitamin B_{12} derivatives. [7–9]

2.2 Synthesis of Salophen Ligands

Salophen ligands are readily synthesized by the condensation of *o*-phenylenediamine and two equivalents salicylaldehyde. Incorporation of metal ions is facile, and many different metals can be successfully introduced (Cu, Co, Ni, Fe, Mn and Zn).[10–11] To obtain our desired compound, **2.4**, refluxing ligand **2.3** in ethanol with cobalt(II) acetate gives high conversion to the desired product, which is easily purified by recrystallization in ethanol (Figure 2.1).

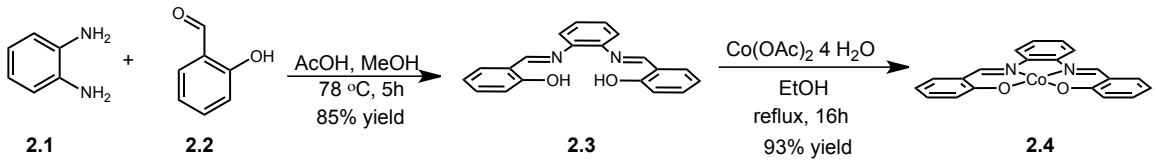


Figure 2.1 Synthesis of cobalt salen **2.4**

Additionally, oxidation to Co(III) species is well known and efficient.[12] Oxidation of complex **4** with iodine gave rapid conversion to the iodo-salophen complex **2.4•I**, tosic acid and acetic acid produced each corresponding cobalt (III) products **2.4•OTs** and **2.4•OAc**, presumably with oxygen as the oxidant. Further, ligand exchange from **2.4•OTs** using aqueous sodium bromide and chloride solutions gave **2.4•Br** and **2.4•Cl** in quantitative yields (Figure 2.2).

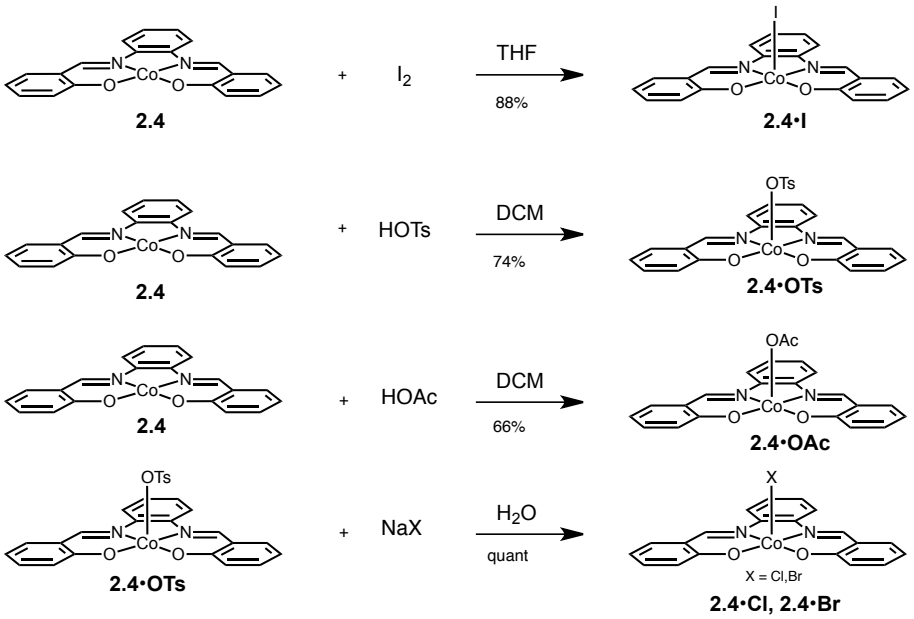
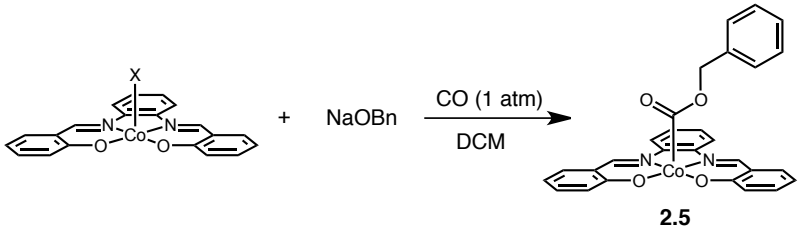


Figure 2.2 Synthesis of Co(III)salophen complexes

2.3 Redox-Neutral Synthesis of Alkoxycarbonyl Cobalt Salophen

Seminal work from Costa and Mestroni in the 1960s reported the first examples of carbonylation reactions with alcohols using vitamin B_{12} model ligand systems.[13–15] A number of simple alkoxy substituents were incorporated under a carbon monoxide atmosphere in alcohol solvent (MeOH, EtOH, *i*PrOH), however no yields were reported. Mimicking Costa and Mestroni's procedures, we initially examined the reactivity of each



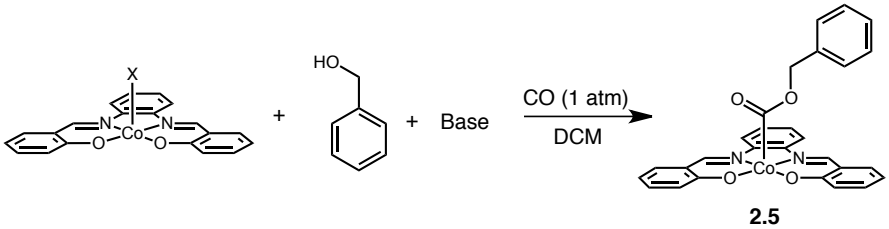
2.5

X	Yield
I	16%
OTs	0%
Cl	0%
Br	0%
OAc	0%

Table 2.1 Carbonylation of **2.4•X** with NaOBn

complex **2.4•X** by adding a 1 M sodium benzyloxide solution in benzyl alcohol under 1 atm of carbon monoxide. Under these conditions, only the **2.4•I** provided any desired product (Table 2.1).

Next, different bases were tested to form the alkoxide (Table 2.2). Inorganic bases such as sodium phosphate showed promise with salen ligands (see Chapter 3) though did little to improve conversion with salophen. Exchanging sodium for sodium hydride (used to generate the alkoxide) increased the yield of **2.5** significantly, however, no optimization



2.5

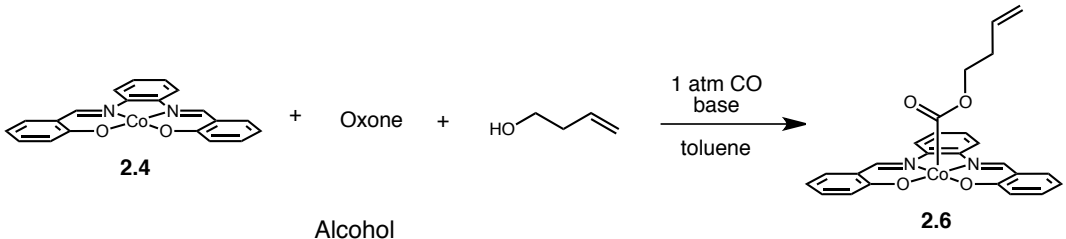
X	Base	Yield
I	Na	16%
I	NaH	30%
OTs	Na_3PO_4	19%

Table 2.2 Carbonylation of **2.4•X** with alternative bases

improved the conversion above 30%. With little success forming the alkoxycarbonyl complex from the **2.4•X** complexes, focus shifted to find alternative methods.

2.4 In Situ Oxidation/Carbonylation of Cobalt Salophen

While optimizing the redox neutral carbonylation, Peng, Fu and coworkers reported a one-step oxidation/carbonylation from Co(II)salen.[16] They achieved the formation of a methoxycarbonyl-Co(III)salen using this method and methanol as a co-solvent with toluene. Unfortunately, requiring the alcohol to act as a co-solvent limits the possible scope of this reaction, restricting studies to cheap commercially available



Alcohol equiv.	Base	Yield
1	–	28%
3	–	45%
5	–	69%
7	–	70%
9	–	72%
5	NaOH	33%
5	KOH	50%
5	$NaHCO_3$	0%

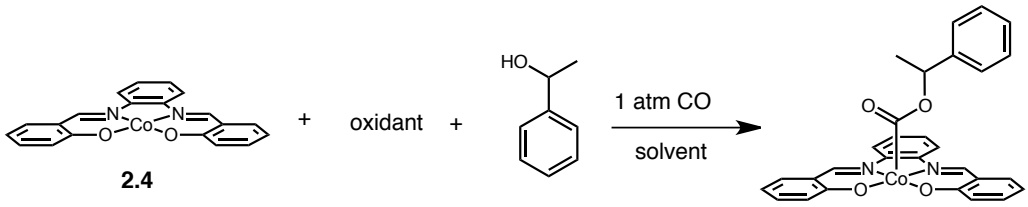
Table 2.3 Test of alcohol stoichiometry required for carbonylation of **2.4**

compounds. Our initial focus was to test conditions to reduce the required alcohol (Table 2.3). Starting from a relatively simple primary alcohol, we observed good yields using 5-9 equivalents of 3-buten-1-ol. Addition of base to this reaction uniformly gave inferior yields.

To optimize this process, reactions were run for 48 h in a carbon monoxide atmosphere achieved by bubbling CO through the solvent using a balloon. Attempts to

increase reaction rate by heating reactions to 50 °C and 70 °C caused decomposition after 24 h. Further optimization was studied using a secondary alcohol, 1-phenylethanol. Initial studies showed a greater dependence on alcohol equivalents with the higher steric hinderance, but through optimization of solvent and oxidant (Table 2.4) to DCE and $K_2S_2O_8$, respectively, we were able to achieve a 72% yield of the desired product while requiring only 3 equivalents of alcohol. Overall, we were able to reduce the excess of oxidant, alcohol and reaction time from 5 equiv, 9 equiv, and 48 h to 4 equiv, 3 equiv and 16 h, respectively.

These alkoxycarbonyl cobalt complexes were observed to be air and silica column stable as well as moderately tolerant to light exposure. The one-pot oxidative method is

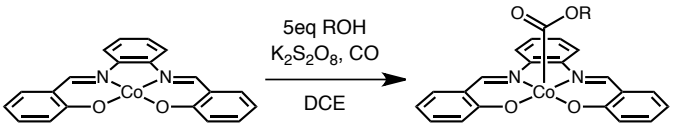


2.4 + oxidant + → **2.7**

Oxidant	Ox. equiv	Solvent	OH equiv	Yield
Oxone	5	Toluene	5	39%
Oxone	5	Toluene	7	66%
Oxone	5	Toluene	9	71%
Oxone	5	DCE	9	86%
Oxone	5	Benzene	9	74%
Oxone	5	$CHCl_3$	9	50%
Oxone	5	THF	9	33%
Oxone	5	CH_3CN	9	0%
$K_2S_2O_8$	4	DCE	3	72%
$Na_2S_2O_8$	4	DCE	3	69%
Oxone	4	DCE	3	69%
$(NH_4)_2S_2O_8$	4	DCE	3	35%

Table 2.4 Reagent optimization of in-situ oxidation/carbonylation of **2.4**

quite general and was explored extensively with the salophen ligand system, providing a wide variety of functionalized products in moderate to excellent yields (Table 2.5).[17]



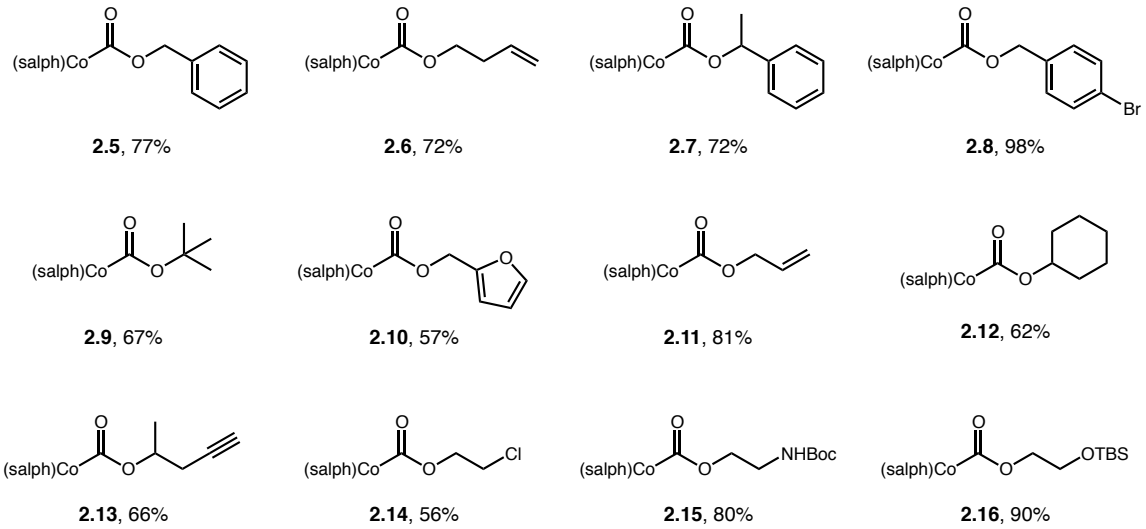


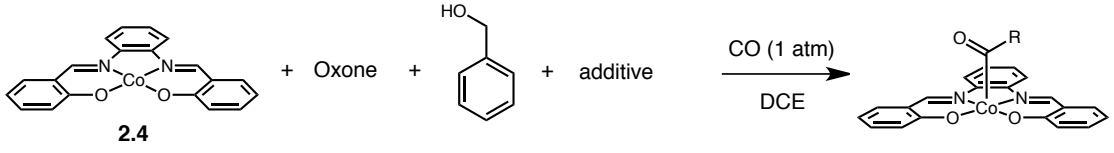
Table 2.5 Scope of oxidative carbonylation

The reaction tolerated a variety of 1º, 2º and 3º alcohols, with comparable yields despite increased steric hindrance (56–98% yield). An electron-rich furan group is incorporated without incident (**2.10**, 57% yield). The reaction tolerates common functional handles such as olefins (**2.6** and **2.11,** 72-81% yield), alkynes (**2.13**, 66%), aryl and alkyl halides (**2.8** and **2.14**, 56–98% yield). In addition, protected alcohols and amines are efficiently incorporated to give differentially functionalized products (**2.15** and **2.16**, 80–90% yield). The broad tolerance of common functional groups demonstrates the applicability of this method to a wide scope of complex alcohols. Only strongly Lewis

basic groups such as pyridines and unprotected amines interfere with the carbonylation reaction, resulting in reaction breakdown.

Unfortunately, attempts to expand this carbonylation protocol beyond alcohols were less successful. Initial efforts to carbonylate amines under similar conditions all met with failure, likely due to the amines acting as an axial ligand. Pattenden and coworkers were able to utilize carbamoyl chlorides under their reductive conditions to make the aminocarbonyl products, however under our carbonylative conditions no desired product was formed.[18] Significant experimentation with additives and conditions provided no improvement, therefore alternative conditions will need to be developed to achieve this transformation.

Additionally, studies of the carbonylation in the presence of other reagents were performed. As thiols and phenols will be employed in later applications of this methodology (see Chapter 1), it is important that there will not be a competitive reaction that inhibits or interferes with the desired transformation. Auspiciously, carbonylation of phenols and thiols, themselves, was unsuccessful. Under optimal conditions, no carbonylated compounds were detected in the presence of thiols or phenols (Table 2.6).



2.4

BnOH	additive	Yield
-	phenol	0%
-	dimethylthiophenol	0%
3 equiv	-	70%
3 equiv	dimethylthiophenol	29%
3 equiv	triisopropylthiophenol	67%

Table 2.6 Competition studies for carbonylation of **2.4**

Unfortunately, addition of thiols into carbonylation reactions with benzyl alcohol initially showed inhibition of product formation. However, increasing the steric hinderance around the thiol mitigated this issue (2,6-dimethylthiophenol to 2,4,6-triisopropylthiophenol).

Because thiols are not competitively carbonylating, the inhibition is likely due to rapid oxidation of thiol to disulfide, consuming the Oxone.[19,20] Increased steric bulk in the triisopropylthiophenol slows dimerization, allowing carbonylation to proceed. With a robust method to form these complexes accomplished, we began a detailed investigation into the structure of the carbonylated species.

2.5 Structural Studies

Before our studies, any simple alkoxycarbonyl cobalt complexes reported were characterized only by IR, UV-Vis spectroscopy and in rare cases NMR. We performed more extensive analysis of the alkoxycarbonyl complexes, including ^{1}H NMR, ^{13}C NMR, mass spectrometry, X-ray diffraction and IR spectroscopy.

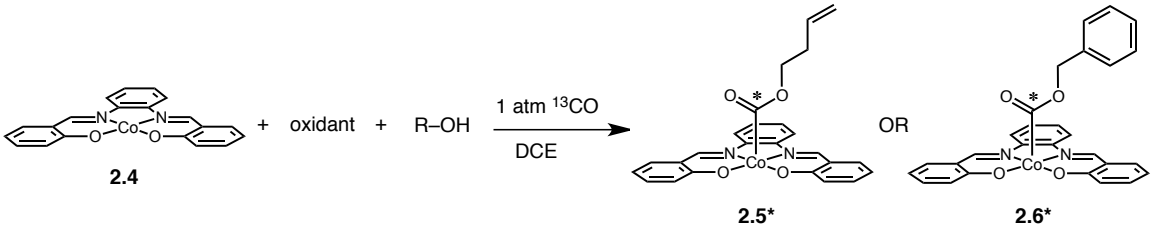


Figure 2.3 Carbonylation of **2.4** with ^{13}CO

The paramagnetic Co(II) complexes cannot be effectively be characterized by ^{1}H NMR due to broad peaks that are nonsensical by integration. The diamagnetic Co(III) complexes are symmetrical in solution by NMR, potentially indicating facile rotation about

the Co–C bond. The α-oxy C–H's show distinct resonances in the ^{1}H NMR spectrum at 3.39–5.83 ppm, while in most cases the β-oxy C–H's were shifted upfield due to their proximity to the extended aromatic ligand framework (e.g. **2.7:** α-oxy C–H, 3.44 ppm and β-oxy C–H, 0.96 ppm.

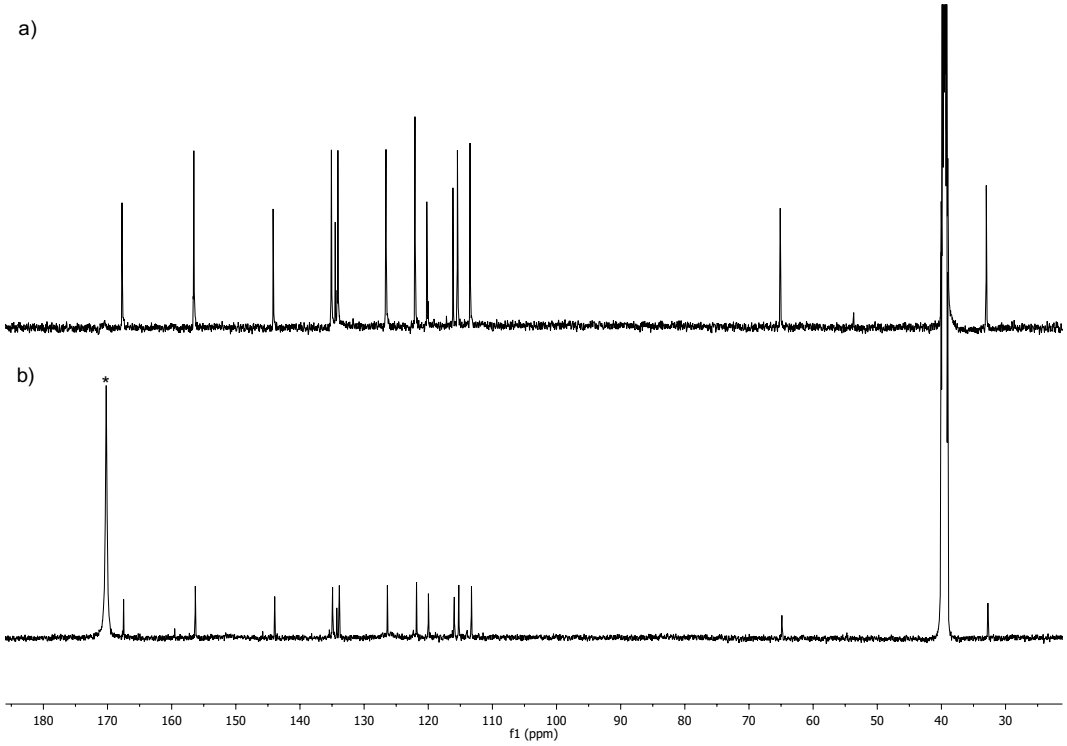


Figure 2.4 ^{13}C NMR of (a) complex **2.5** and (b) complex **2.5***

Analysis by ^{13}C NMR clearly shows resonances for all ligand and alkyl group carbons. The carbonyl carbon appears as a small, broadened peak at approximately 170–172 ppm. This resonance was difficult to identify for most complexes, in particular those with lower solubility. To address any ambiguity regarding the identity of this resonance, we implemented a ^{13}C-enriched carbon monoxide atmosphere (Figure 2.3) and observed significant enhancement of the peak at 172.1 ppm for **2.5*** (Figure 2.4) and 170.1ppm for **2.5*** (Figure 2.4)(measured in d_6-DMSO). Additionally, all products have a distinct IR

absorption at 1662–1693 cm^{-1}, characteristic of the alkoxycarbonyl group, when ^{13}C-carbon monoxide was used this distinctive stretch disappeared and a new stretch was observed at 1580 cm^{-1} consistent with the labeled CO.[21]

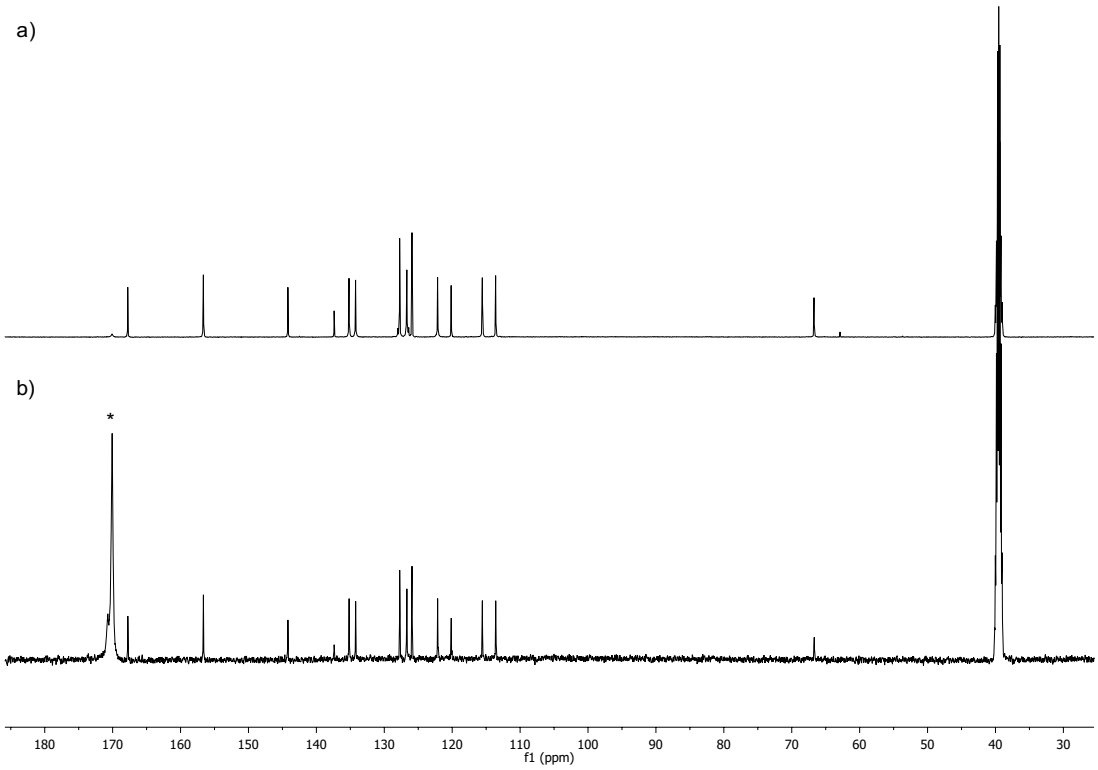


Figure 2.5 ^{13}C NMR of (a) complex **2.6** and (b) complex **2.6***

In order to obtain detailed structural information, X-ray diffraction studies were carried out. Crystals of 1-phenethyl salophen product **2.7** were grown from a MeOH solution by evaporation. In the crystals, product **2.7** adopted a distorted octahedral geometry with a molecule of methanol opposite the alkoxycarbonyl substituent (**2.7•MeOH**, Figure 2.6). The heteroatoms of the salophen ligand are nearly coplanar, and the cobalt atom is displaced by 0.055 Å above this mean plane toward the apical carbonyl group (C1A). The Co–C bond length is 1.894(2) Å, which is slightly shorter than the typical

Co–C bond lengths in corresponding *alkyl* cobalt complexes (~1.96–2.04 Å) and is consistent with previous acyl and alkoxycarbonyl cobalt structures.

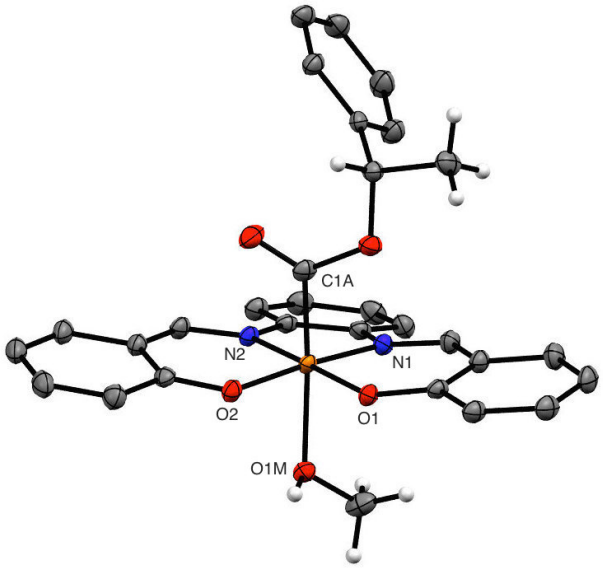


Figure 2.6 X-ray crystal structure of **2.7•MeOH** with thermal ellipsoids at the 50% probability level. Compound crystallizes as a racemate, only one enantiomer shown for clarity. Selected bond lengths [Å] and angles [º]: Co–C1A 1.894(2), Co–O1 1.904(1), Co–O2 1.888(1), Co–N1 1.892(2), Co–N2 1.889(1), Co–O1M 2.161(1); O1–Co–O2 86.2, O1–Co–N1 94.0, N2–Co–O2 94.9, N2–Co–N1 84.8, O1–Co–C1A 91.9, O2–Co–C1A 90.5, N1–Co–C1A 94.1, N2–Co–C1A 90.2, C1A–Co–O1M 176.3.

We also obtained suitable crystals from a solution of *p*-bromobenzyl salophen product **2.8** in pyridine/water (Figure 2.7) and in DCM (Figure 2.8). The solid-state structure shows a distorted octahedral geometry with an apical pyridine substituent and a co-crystallized molecule of pyridine (not shown) that does not directly interact with the cobalt atoms (overall formula: (**2.8•py**)$_2$(py)(H_2O)). A water of crystallization acts as a hydrogen bond bridge between the salophen oxygen atoms of adjacent molecules in the unit cell, with each ligand engaging in one H-bond. Again, the N_2O_2 atoms are nearly coplanar and the cobalt atom is displaced by only 0.010 Å above this mean plane toward the alkoxycarbonyl group. This is consistent with the stronger *trans*-influencing properties

of pyridine, resulting in a slightly longer Co–C bond (1.900(3) Å). Interestingly, when crystals were grown of complex **2.8** in methylene chloride, a dimerized product was observed (Figure 2.8). Unfortunately, the quality of the crystal was very low, so bond lengths and angles are not suitable for comparison due to the large estimated standard deviations of the structure.

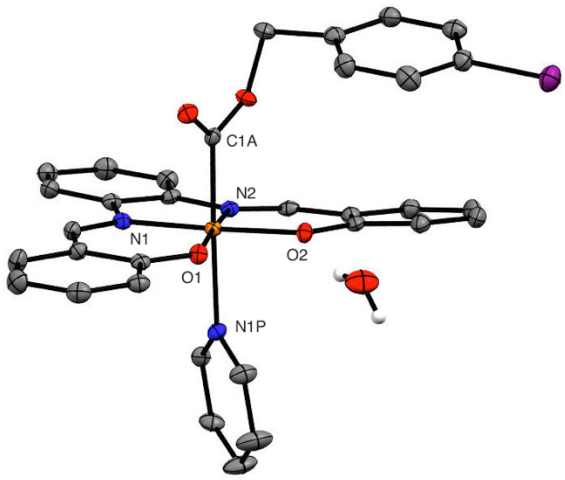


Figure 2.7 X-ray crystal structure of (**2.8•py**)$_2$(py)(H_2O) with thermal ellipsoids at the 50% probability level. One co-crystallized pyridine molecule is omitted for clarity. Selected bond lengths [Å] and angles [º]: Co–C1A 1.900(3), Co–O1 1.890(2), Co–O2 1.903(2), Co–N1 1.891(2), Co–N2 1.896(2), Co–N1P 2.119(2); O1–Co–O2 83.2, O1–Co–N1 96.1, N2–Co–O2 96.0, N2–Co–N1 84.9, O1–Co–C1A 90.7, O2–Co–C1A 88.7, N1–Co–C1A 88.9, N2–Co–C1A 92.8, C1A–Co–N1P 177.6.

There are only four previous structurally characterized acyl- or alkoxycarbonyl-cobalt species with planar tetradentate Schiff base ligands related to those used here, all of which were pentacoordinate complexes with square pyramidal geometry.[16,22–24] The impact of five- versus six-coordinate geometry appears to be minimal, with no major changes to the metrics of the complexes. Although, it is likely that previously reported complexes are

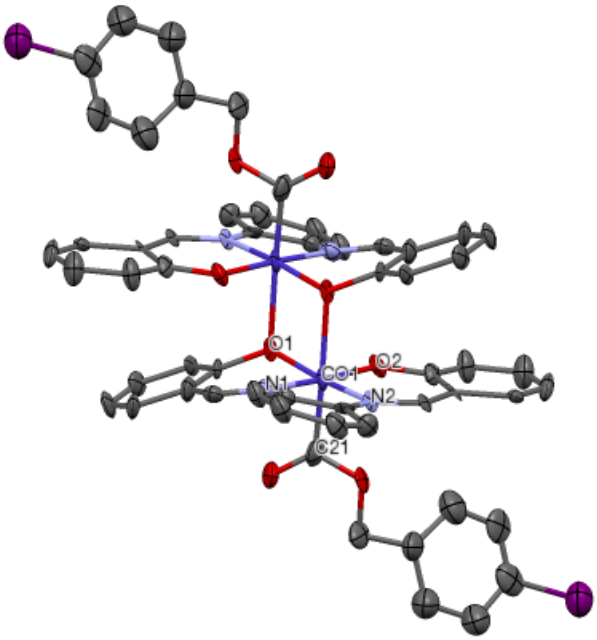


Figure 2.8 X-ray crystal structure of (**2.8**)$_2$(CH_2Cl_2) with thermal ellipsoids at the 50% probability level. One methylene chloride molecule is omitted for clarity.

pentacoordinate and do not dimerize due to the steric bulk of the *tert*-butyl substituents utilized. Of particular note, the measured Co–C bond lengths are all within 0.03 Å of each other (1.878–1.906 Å), and the bond lengths reported here also lie within this range. The pentacoordinate system most similar to our complexes is the methoxycarbonyl cobalt di-*tert*-butylsalen complex was reported by Fu and coworkers.[16] Although this complex is a salen ligand system and no axial ligand is present, the crystal structure had a nearly identical Co–C bond length (1.895(4) Å), again highlighting the minimal impact of the precise nature of the ligand framework and the presence or absence of a donor opposite the alkoxycarbonyl group.

2.6 Transesterification Reactions

During the course of our carbonylation optimization, we noted the unexpected formation of a methoxycarbonyl product during the synthesis and isolation with other aliphatic alcohol substrates. Initial concerns of methanol impurities in DCE were confirmed and purification by distillation over 5 Å sieves reduced the methoxycarbonyl product in the crude reaction mixture. However, even when the methoxycarbonyl product was not observed upon completion of the reaction, it was (often) detected after purification. Ultimately, we determined that the by-product was being formed primarily during the purification process in the presence of silica gel and methanol in the eluent. This was confirmed by running a previously pure compound (purified in a non-methanolic column) though a silica gel column and eluting with a 10% methanol solution in DCM. After the column, methoxycarbonyl product was observed by ^{1}H NMR. Previous reports of related transesterification reactions of alkoxycarbonyl metal complexes have typically occurred under neutral or basic conditions, and the majority involve bound CO ligands in the exchange.[25–29] The unusual nature of this reaction and its potential importance for future investigations of catalytic chemistry with competing alcohol substrates led us to investigate

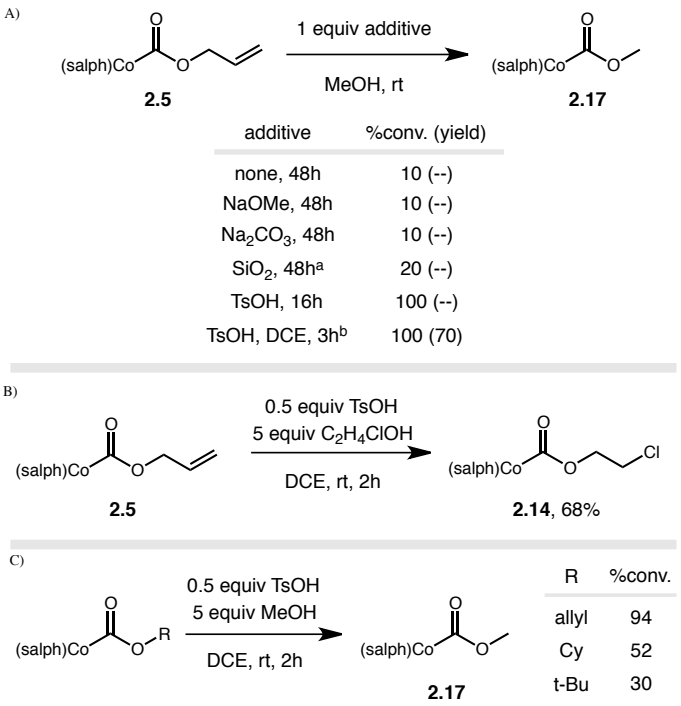


Table 2.7 Transesterification of alkoxycarbonyl products. [a]50 mg SiO_2. [b]0.5 equiv TsOH, 5 equiv MeOH in DCE

this transesterification reaction further (Table 2.7). The reaction of salophen complex **2.6** in methanol is representative, leading to 10% conversion over 48 h. The alcohol exchange was neither enhanced nor inhibited by base, however it was indeed accelerated by the addition of silica gel. Using the significantly more acidic TsOH, in substoichiometric amounts, full conversion was observed in considerably less time (Table 2.7, entry 5). Additionally, using DCE as the reaction solvent and catalytic TsOH, methoxycarbonyl product **2.17** could be isolated in 70% yield after 3 h, with 100% conversion and some decomposition. This reaction was then tested with 2-chloroethanol, affording complex **2.14** in 68 % yield (Table 2.7, B), an improvement over the yield of the direct carbonylation

procedure. This transformation suggests an alternative route to target carbonylated complexes that are too sensitive for the carbonylation conditions.

When comparing the reaction rates of 1º, 2º and 3º alcohol-derived starting materials with methanol as the nucleophile (Table 2.7, C) we observed a clear trend of decreasing reactivity with increasing steric bulk, and only the reaction of the primary substrate went to completion over the course of 2-3 h. This suggests either a dissociative mechanism triggered by protonation of the alkoxy oxygen, or an associative mechanism where the alcohol reacts with the carbonyl group upon protonation. Both associative and dissociative processes have been previously proposed and limited information exists for acid-catalyzed exchanges of this type. To the best of our knowledge, this is the first example of a transesterification process with a Co(III) species. Most examples of transesterification with cobalt have been demonstrated using dicobalt octacarbonyl complexes or compounds with multiple bound CO ligands.[30,31]

2.7 Homolysis Studies

As alkoxycarbonyl cobalt(III)salophen complexes were previously difficult to synthesize, the Co–C bond strengths have not been studied to the same extent as their alkyl counterparts. Work by Halpern and others have shown computational bond strengths of alkyl complexes but the BDE of alkoxycarbonyl complexes have yet to be studied.[9,32,33] To determine whether this bond could be photolytically cleaved, we first examined the UV-VIS of the alkoxycarbonyl Co(III) salophen **2.7** (Figure 2.9). The spectrum of **2.7** showed absorption maxima at 320 and 410 nm, consistent with Co(II) salophen as well as an

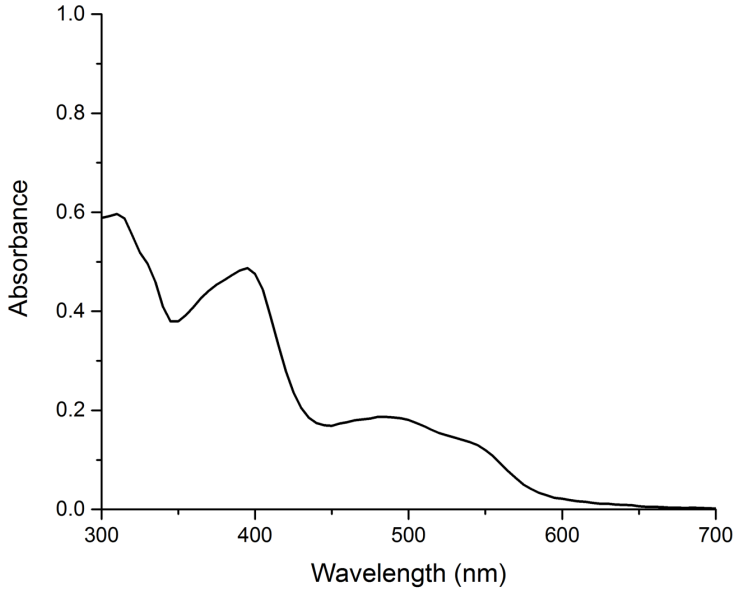


Figure 2.9 UV-Vis of **2.7** in $CHCl_3$

absorption from 450-570 nm. Since there is a significant absorbance in the visible range, LEDs were used to excite the Co–C bond. To determine whether there is photolytic cleavage of the Co–C bond, 1-phenethylaloxycarbonyl (**2.7**) was subjected to irradiation using green LEDs (emission at 510-520nm) in the presence of the known radical trapping agent, TEMPO (Figure 2.10). When exposed to high intensity light of the correct wavelength, the weak Co–C bond should homolyze to give Co(II)salophen **2.4** and acyl radical **2.18**. Rapid decarboxylation of the acyl intermediate affords the benzylic radical **2.19** which will react with TEMPO to yield the trapped product **2.20**. Due to the stability of benzylic radical **2.19** decarboxylation is faster than the combination of **2.18** and TEMPO, as measured by Newcomb, no carbonate byproduct is observed.[34–37] When a less stable radical would be formed (such as ethyl radical), Pattenden and coworkers observed

carbonate products under similar reaction conditions.[38] These radical trapping reactions were tested with three substrates (Table 2.8).

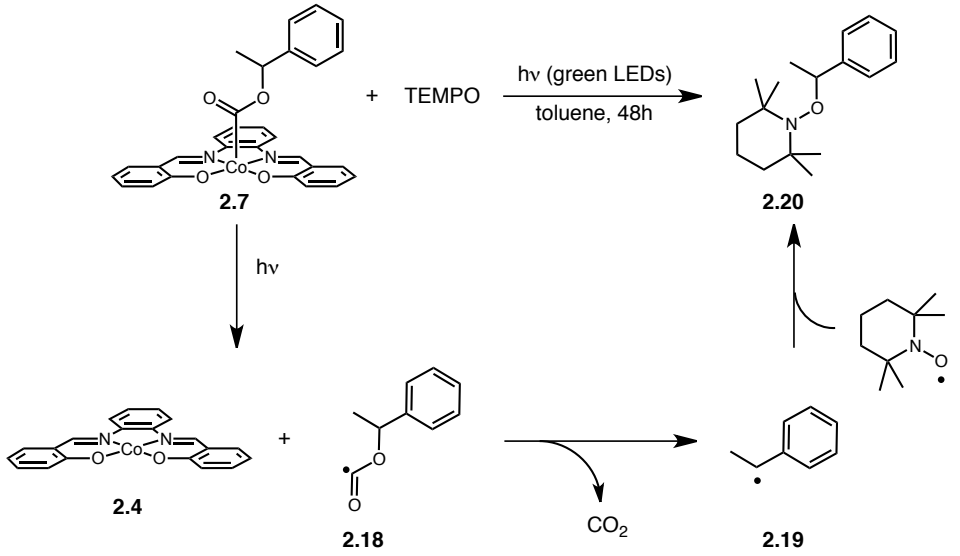
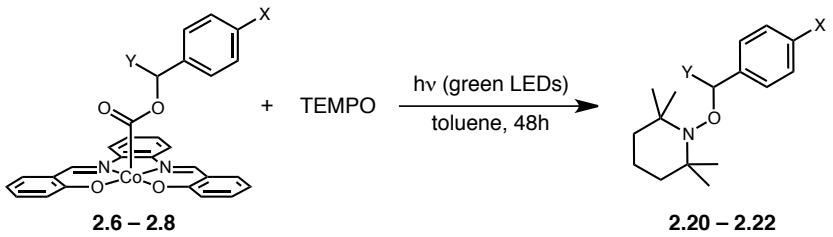


Figure 2.10 Homolysis of **2.7** and TEMPO trapping to form **2.20**

A modest yield of 28% was achieved with the irradiation of **2.6**, whereas 49% and 50% were obtained when irradiating **2.7** and **2.8**, respectively. This is likely due to the relative stability of the benzylic radical formed, with the primary radical least stabilized, the primary, electron poor radical more stabilized, and the secondary radical most stabilized. Most notably, the *p*-bromobenzyl TEMPO trapped product formed from



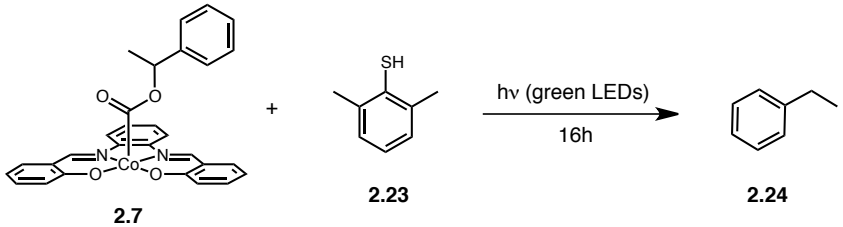
X	Y	Yield
H	Me	**2.20**, 49%
Br	H	**2.21**, 50%
H	H	**2.22**, 28%

Table 2.8 Homolysis-decarboxylation-TEMPO trapping reactions

excitation of **2.8** retains the bromide. As this radical behavior is orthogonal to traditional metal-catalyzed reactions, this method has potential to be highly complementary when used in a synthesis plan.

2.8 Hydrogen Atom Transfer/Reduction

Next, we probed the compatibility of this system with HAT reagents, focusing on thiols based on appropriate X–H bond dissociation energies (S–H BDE = 82 kcal/mol for thiophenol, C–H BDE = 86 for ethyl benzene).[39–43] Irradiation of salophen complex **2.7** with stoichiometric quantities of 2,6-dimethylthiophenol formed our desired reduced product **2.24** in a 30% yield (Table 2.9). A solvent screen was performed, and dichloromethane was found to be the optimal solvent, with benzene derivatives and chlorinated solvents working moderately well. Solvents examined that gave <5% yield include DMF, CH_3CN, dioxane, and DME.

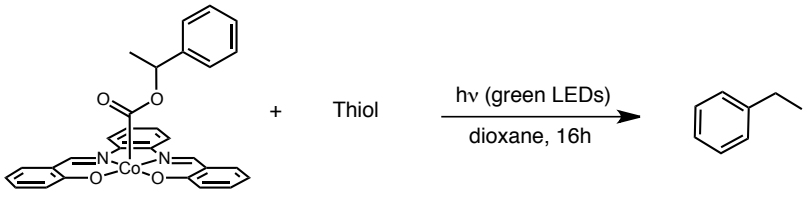


Solvent	Yield
DCM	30%
Benzene	24%
Chlorobenzene	23%
THF	17%
Cyclohexane	0%

Table 2.9 Homolysis and reductive radical trapping with 2,6-dimethylthiophenol

Preliminary irradiation reactions with thiols proved to be significantly more air sensitive than originally anticipated. Early experiments were set up in 8 mL vials and degassed, however, they were found to be highly inconsistent and generally low yielding.

Switching from vials to Schlenk tubes improved yields considerably and additional use of freeze-pump-thaw cycles for rigorous degassing was also deemed necessary. One likely cause of this sensitivity is due to the rapid dimerization of thiols to the corresponding disulfide in the presence of oxygen, as previously discussed. This was confirmed by adding steric bulk to the ortho positions of the thiol; increasing steric hindrance going from thiophenol to 2,6-dimethylthiophenol to 2,4,6-triisopropylthiophenol was met with an increase in the yield of ethyl benzene (Table 2.10).



2.6 **2.24**

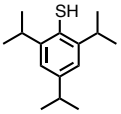
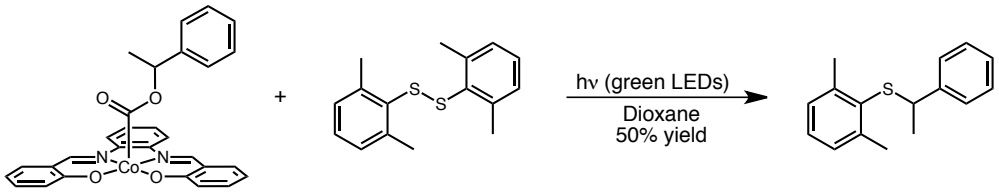
Thiol	Yield
	10%
	15%
	20%

Table 2.10 Study of the effect of increased steric bulk around thiol for HAT

Unfortunately, increasing steric bulk did not sufficiently reduce the rate of disulfide formation to favor HAT. Even using 2,4,6-triisopropylthiophenol, by GC it was observed that all thiol was consumed before **2.6** was fully consumed, even when used in significant excess. Additionally, as reaction times were extended a thioether byproduct **2.26** began to

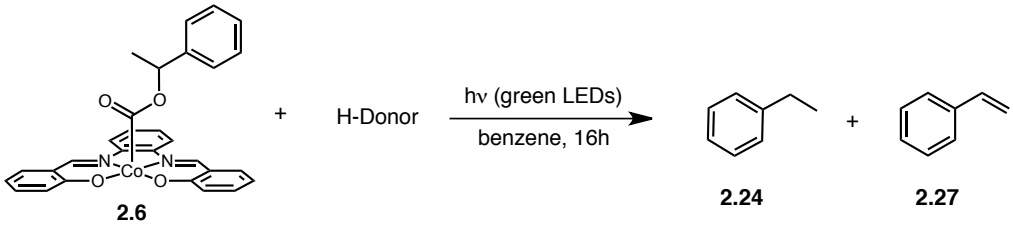
form, which is consistent with addition of the benzylic radical intermediate into a disulfide (Figure 2.11).[44,45]



2.6 **2.25** **2.26**

Figure 2.11 Synthesis of thioether **2.26** by homolysis of **2.6** in the presence of disulfide

We then examined methyl thiosalicylate and 4-nitrothiophenol to test if variations in the electronics had a positive effect, however both were ineffective. As dimerization is a fundamental issue with thiols, we looked into other potential hydrogen atom donors (Table 2.11). Unsurprisingly, cyclohexadiene was not very effective, as HAT from carbon to carbon is significantly slower than that from heteroatoms.[40] Triethylsilane was unexpectedly ineffective and Hunig's base was equally ineffectual.

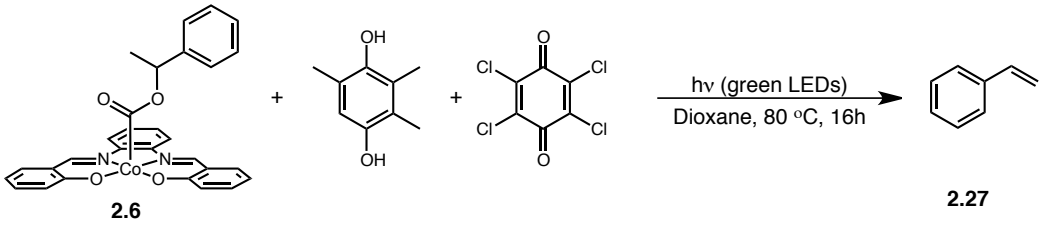


2.6 **2.24** **2.27**

H-Donor	Ethyl benzene	Styrene
Cyclohexadiene	5%	0%
Methyl thiosalicylate	5%	0%
Et_3SiH	0%	0%
Hunig's Base	0%	0%
4–Nitrothiophenol	0%	0%
Tetrafluorohydroquinone	0%	24%
Methylhydroquinone	0%	27%
Trimethylhydroquinone	0%	31%

Table 2.11 Hydrogen atom donor studies

Interestingly, when using hydroquinones that have ideal BDE and redox potentials for HAT,[46] we saw an unexpected styrene product. Perplexed, we first assumed that the hydroquinone was being oxidized to the quinone and the resulting quinone was responsible for the oxidation of the benzylic radical to styrene. Testing the respective quinones under our reaction conditions we found that all reactions failed to produce styrene (Table 2.12).



2.6 2.27

Hydroquinone	Quinone	Styrene
1 equiv	0 equiv	30%
0.5 equiv	0.5 equiv	4%
0 equiv	1 equiv	0%

Table 2.12 Test of quinone and hydroquinone equivalents on styrene formation

Next, we examined the reactions with a mixture of quinones and hydroquinones and again found that whenever quinone was introduced into the reaction, a dramatic decrease in product formation were observed. With this data we consider whether under the reaction conditions that a semiquinone is formed, which abstracts a hydrogen from our benzylic radical forming styrene rather than donating a second hydrogen to be converted into quinone. This is particularly surprising as the BDE of the second hydrogen is significantly lower than the first (~69 kcal/mol vs ~84 kcal/mol for 1,4-benzoquinone)[46] though might be explained by the semiquinone acting as an axial ligand to the Co(II) complex formed by homolysis. If the semiquinone acts as an axial ligand, it is possible that the cobalt is abstracting the hydrogen to form styrene and a cobalt hydride complex. Although, more studies will be required to confirm this hypothesis.

2.9 Lactonization Reactions

As we faced significant challenges to get yields of our desired products above 30%, we shifted focus to another important transformation that our cobalt catalyst would facilitate, carbonylation-lactonization of alcohols. Pattenden and coworkers reported a lactonization reaction to form alpha-methyl butyrolactones; however, due to the harsh conditions (reflux, Hg lamp, etc.) only the isomerized product 3-methyl-2-furanone was observed. Our goal was to perform this transformation under mild conditions and be able to tune the catalyst and conditions to selectively form either the reduced, eliminated or isomerized products. Preliminary studies used salophen complexes carbonylated with butenol as it is commercially available and readily formed the alkoxycarbonyl product (Figure 2.12). However, we quickly observed how volatile the products of homolysis were and how that limited our ability to isolate and quantify reaction products. Thus, we synthesized **2.31** and **2.32** which carbonylated well and whose products of homolysis would be less volatile and potentially isolable. Unfortunately, again no cyclized product was

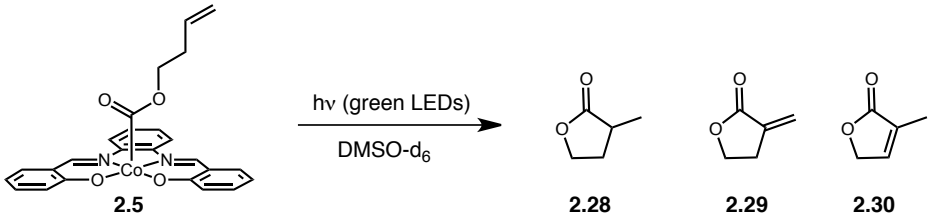
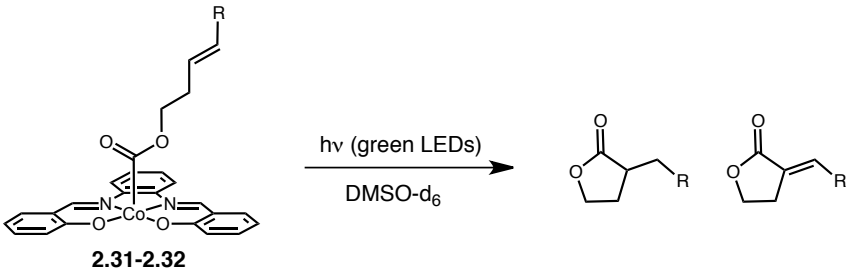


Figure 2.12 Synthesis of butyrolactones by homolysis of **2.5**

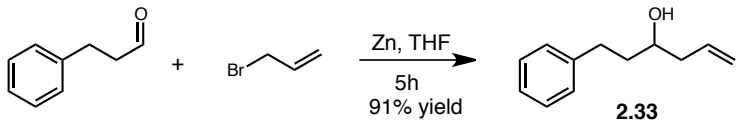


2.31-2.32

R	Reduced pdt	Eliminated pdt
Phenyl	0%	0%
Methyl	0%	0%

Table 2.13 Lactonization reactions from **2.31** and **2.32**

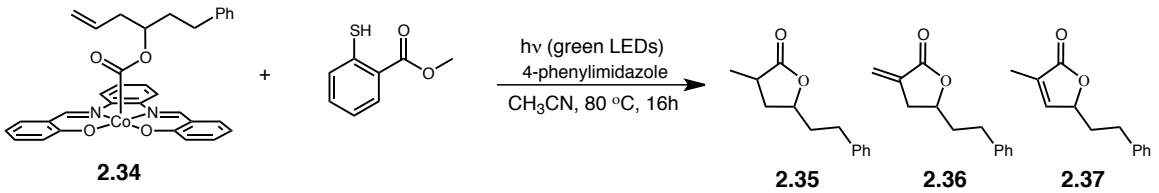
observed (Table 2.13). Alternatively, we synthesized a secondary alcohol with a terminal alkene to study further. Synthesis of **2.33** was achieved via a Barbier reaction between allyl bromide and hydrocinnamaldehyde (Figure 2.13).[47]



2.33

Figure 2.13 Synthesis of **2.33**

Standard carbonylation conditions gave alkoxycarbonyl complex **2.34** in good yield (68%). Excitation of the Co–C bond is expected to produce lactone products via a 5-*exo*-trig cyclization which should be faster than decarboxylation.[48] In the presence of a H-donor, reduced product **2.35** would be the expected product, however, the β-hydrogen eliminated product **2.36** and the isomerized eliminated product **2.37** are also possible. Our initial

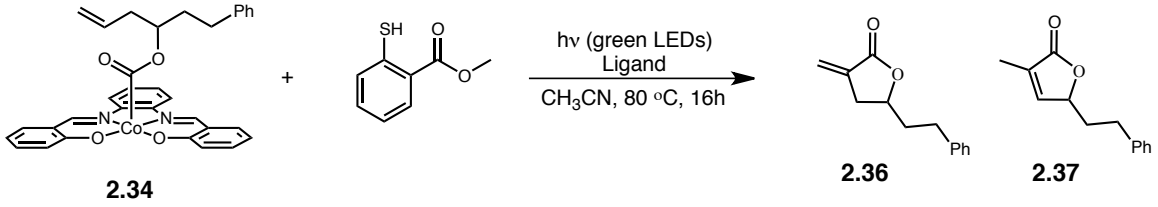


2.34 **2.35** **2.36** **2.37**

Light Source	**2.36**
Green LEDs	35%
All lights	35%
CFL	26%
Blue LEDs	22%

Table 2.14 Homolysis-lactonization of **2.34** with various light sources

studies tested what light source would be most efficient at homolysis (Table 2.14). Clearly, green LEDs emit the best wavelength of light for homolysis of the C–Co bond in **2.34**. Interestingly, even in the presence of a H-donor we observe solely the hydrogen eliminated product **2.36** and no reduced product. To investigate this phenomenon further, we next investigated numerous ligands to see their effect on this selectivity (Table 2.15). From our

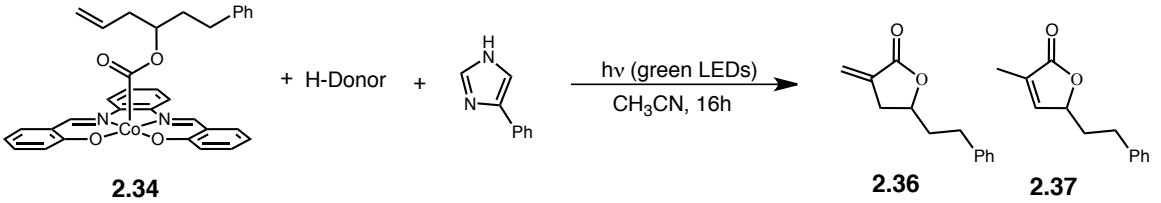


2.34 **2.36** **2.37**

Ligand	**2.36**	**2.37**
4-phenylpyridine	29%	0%
PCy_3	24%	4%
–	22%	0%
4-phenylimidazole	19%	0%
KCN	18%	0%
Tetrabutylammonium cyanide	16%	0%

Table 2.15 Ligand screen for lactonization reactions

ligand screen it appears that under these conditions, all ligands tested favor eliminated product **2.36** to various extents with PCy_3 being the only ligand to form any isomerized product **2.37**, albeit only in trace amounts. Starting from conditions (H-donor, solvent,

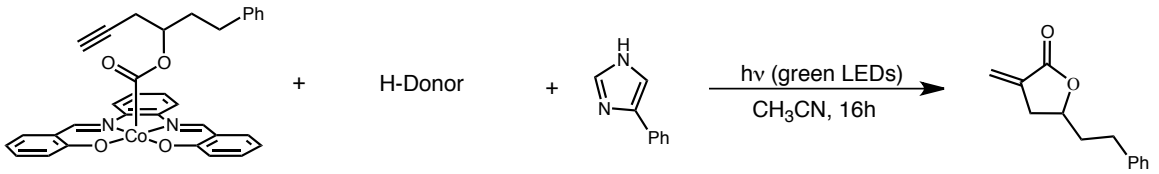


2.34 **2.36** **2.37**

H-Donor	**2.36**	**2.37**
Tetrachlorohydroquinone	0%	14%
iPr_3SiH	32%	0%
Ph_3SiH	40%	0%
Et_3SiH	51%	0%

Table 2.16 H-donor screen for lactonization reactions

temperature and ligand) optimized by Dr. Esmat Sodagar, we observed that reaction run solely with green LEDs produced the same amount of **2.36** was when all light sources are used together. Again, no reduced product was observed, so a change in hydrogen atom donor was examined (Table 2.16). Testing a hydroquinone gave an interesting result of



2.38 **2.36**

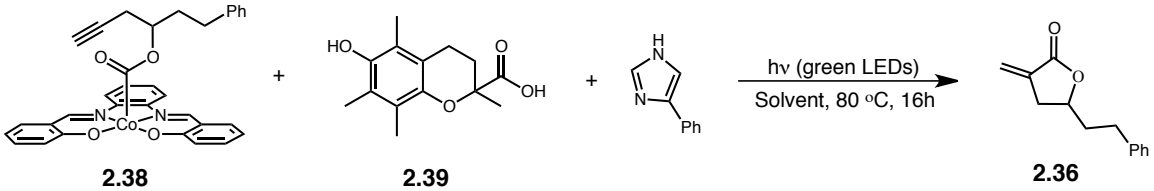
H-Donor	**2.36**
Trolox	9%
Cl_3SiH	0%
iPr_3SiH	0%
Ph_3SiH	0%
Et_3SiH	0%

Table 2.17 Examination of H-donors for lactonization from complex **2.38**

exclusively the isomerized product **2.37**, although, only in modest yield. Additionally, reactions with silanes gave good conversion to eliminated product **2.36** with triethyl silane with our highest conversion at 50% yield. However, with all the H-donors tested, no

reduced product. was ever observed, either because the H-donor are insufficiently reactive or because elimination is faster than HAT.

To test this, we decided to synthesize a compound that could cyclize but not β-hydrogen eliminate. A homopropargylic alcohol was synthesized by a Grignard reaction with propargyl magnesium bromide and catalytic $HgCl_2$.[49] Carbonylation under optimized conditions successfully gave product **2.38** in 63% yield. Irradiation of **2.38** then forms an acyl radical which will undergo a 5-*exo*-dig cyclization resulting in a primary radical that can not β-hydrogen eliminate (Table 2.17). From our H-donor examination, it is clear that silanes are not suitable for this transformation but Trolox (**2.39**) shows some potential. As this is our first indication of H-donation after cyclization, we attempted to optimize our conditions further with a solvent screen (Table 2.18). Some improvement in yield was observed using dioxane and DME, however, still at very low yields. Further study into lactonization reactions are discussed in Chapter 3 and 4 where additional insight was gained.



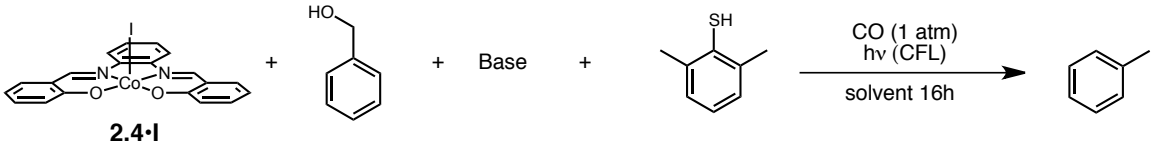
2.38 **2.39** **2.36**

Solvent	**2.36**
Dioxane	14%
DME	14%
THF	9%
2-MeTHF	6%
TBME	5%
Chlorobenzene	5%
Benzene	0%

Table 2.18 H-donor screen for lactonization reaction

2.10 One Pot Reactions

With established methods for carbonylation and homolysis, we shifted our focus to combine these steps into a one pot, catalytic reaction. In our preliminary studies, we utilized **2.4•**I as our Co(III)salophen source and benzyl alcohol as our alcohol because it

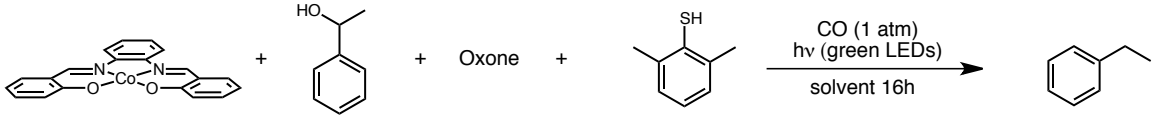


2.4•I

(a) Base	Toluene	(b) Solvent	Toluene
NaOH	0%	Benzene	1%
KOH	0%	Chlorobenzene	1%
Et_3N	0%	Dioxane	1%
Py	0%	CH3CN	0%
NaH	0%	CHCl3	0%
DBU	0%	DCM	0%
Na_2PO_4	0%	$PhCF_3$	0%
Li_2CO_3	0%	DCM	0%
$CsCO_3$	0%		

Table 2.19 One pot reaction (a) base and (b) solvent studies

efficiently carbonylates and all possible products of the reaction are commercially available compounds. We imagine that the carbonylation will proceed as observed in earlier reactions, the alkoxycarbonyl complex will homolyze and thiol will act as the H-donor (Table 2.19). The thiyl radical produced will be reduced by Co(II) to turn over the catalytic



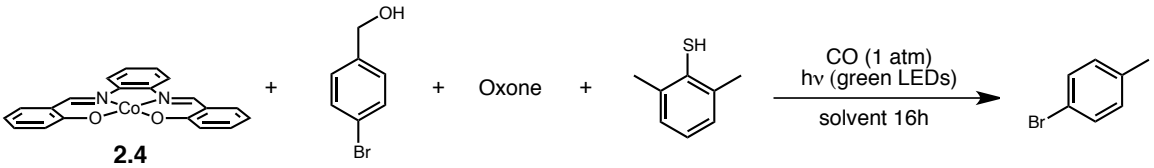
2.4 **2.24**

Solvent	Ethylbenzene	1-phenethylalcohol
Dioxane	1%	94%
Toluene	1%	86%
Benzene	1%	82%
DCM	1%	74%
DCE	1%	74%

Table 2.20 Solvent screen for one pot reaction to form ethylbenzene

cycle, however, all reactions failed. Additionally, one pot reactions were tested from Co(II)salophen (Table 2.20); however, only trace amounts of ethylbenzene were observed by GC and no styrene or other by-products were detected. Possible issues with this reaction are incompatibilities between bases and the thiol, increasing the rate of dimerization and ultimately consuming all possible H-donor before carbonylation has commenced.

Studies were also performed starting from Co(II)salophen as it was more efficient for carbonylation reactions than the Co(III) counterparts. Based on success in the TEMPO trapping reactions, 4-bromobenzyl alcohol was tested (Table 2.21). Unfortunately, again,



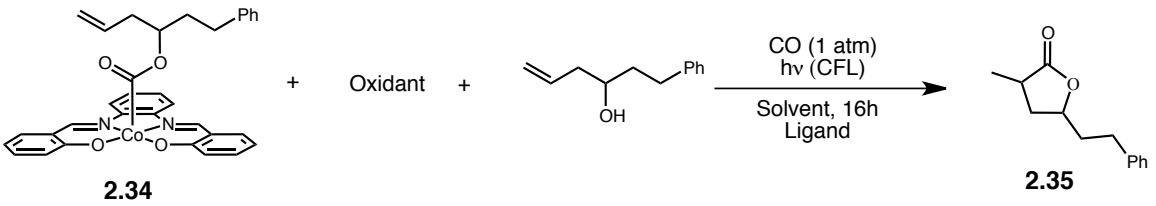
2.4

Solvent	Bromotoluene	4-Bromobenzaldehyde
Benzene	0%	10%
$PhCF_3$	0%	9%
Toluene	1%	9%
DCM	1%	9%
DCE	1%	1%

Table 2.21 One pot reaction to form 4-bromotoluene

only trace amounts of reduced product could be detected. Additionally, there is formation of 4-bromobenzaldehyde identified by GC. This is likely due to either air getting into the reaction or Oxone oxidizing the 4-bromobenzyl alcohol.

Finally, we tested this one-pot method with our lactonization method (Table 2.22). However, under catalytic conditions (20 mol% cobalt loading) we do not detect any product by GC regardless of the solvent, ligand or oxidant tested. The only exception was a trace amount reduced product **2.35** observed when tetrachlorohydroquinone was used and



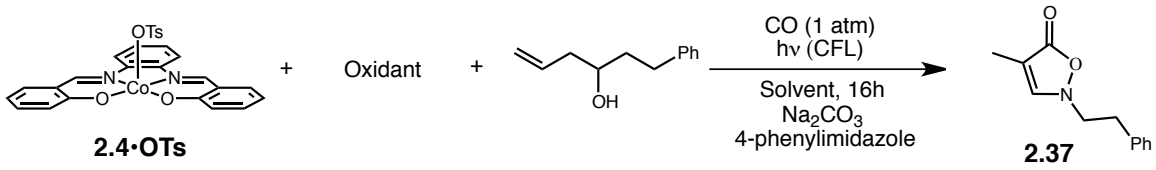
Oxidant	2.35
4-Nitrodisulfide	0%
Tetrachlorobenzoquinone	0%
Tetrachlorohydroquinone	3%

Solvent	2.35
2-MeTHF	0%
THF	0%
Dioxane	0%
DME	0%
TBME	0%
$CHCl_3$	0%

Ligand	2.35
KCN	0%
1-Meimidazole	0%
Py	0%
4-(NMe_2)Py	0%
4-PhPy	0%

Table 2.22 Attempted catalytic reaction conditions. Solvent was CH_3CN, ligand was 4-phenylimiazole and oxidant was tetrachlorobenzoquinone unless otherwise noted

CH_3CN was the solvent. Under similar conditions, the catalytic reaction was attempted starting from **2.4•OTs** (Table 2.23). Similarly, only trace amounts of isomerized product **2.37** were observed when tetrachlorohydroquinone was employed.



Oxidant	Solvent	2.37
Tetrachlorohydroquinone	CH_3CN	0%
Tetrachlorohydroquinone	DCM	2%
Tetrachlorobenzoquinone	CH_3CN	0%
Tetrachlorobenzoquinone	DCM	0%

Table 2.23 Attempted catalysis from Co(III) salophen

As these reactions were set up in 8 mL vials, carbon monoxide was introduced via a balloon, and such addition could have introduced some air which is known to ruin all homolysis reactions. Overall, all of these one-pot reactions failed either due to incompatibilities in reagents or introduction of air into the reaction and more stringent conditions must be employed.

2.11 Enolate Reactions

Looking into an alternative turnover mechanism we investigated the use of enolates (Figure 2.14). Catalyst turnover can be achieved after carbonylation and homolysis of alcohol **2.40** through either the reduction of the radical product **2.41** with electron transfer or recombination with the Co(II) species to form new Co(III) complex **2.42**. By either

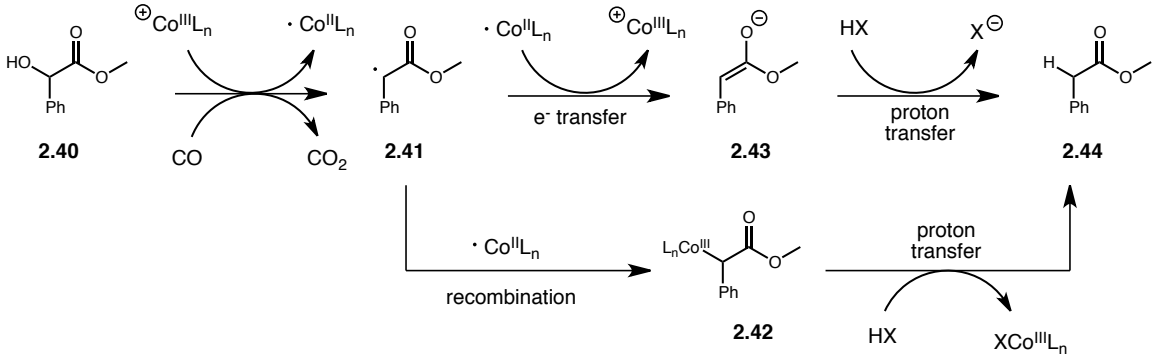
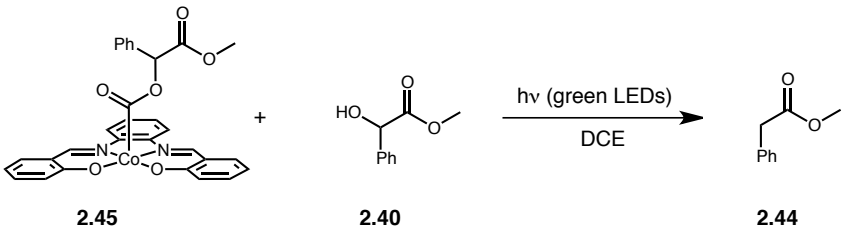


Figure 2.14 Proposed catalytic turnover mechanism by electron transfer or recombination and hydrolysis

method, proton transfer would give reduced product **2.44** and regenerate our Co(III) species. These transformations have been demonstrated on other cobalamin model systems with a (nitrile) or (ester) electron-withdrawing group similar to **2.42**.[5,50,51]



2.45 **2.40** **2.44**

Figure 2.15 Reduction of **2.40** via decarboxylation and enolate intermediate

This concept was tested under our optimal irradiation conditions (Figure 2.15). This reaction was run in both the presence and the absence of excess alcohol **2.40** as well as with the addition of acetic acid as a proton source, in no case was reduced product **2.44** nor a recombined product **2.42** observed. These reaction conditions clearly require a full optimization screen separate from the standard H-donor reaction conditions to form ethylbenzene.

2.12 Conclusions

A carbonylation method has been developed from both Co(III) and Co(II) precursors, requiring only 1 atm of CO and a weak base or oxidant, respectively, and avoiding strong reducing agents and sensitive Co(I) intermediates. Under these mild conditions a wide scope of alcohols can be integrated into these complexes. Full characterization as well as crystal structures and labeling experiments have confirmed incorporation of the carbon monoxide moiety. Interesting reactivity was studied with the transesterification under acidic conditions. Irradiation experiments with TEMPO confirmed the Co–C homolysis to form a radical intermediate and fast decarboxylation under visible light excitation. Studies into HAT demonstrated a clear dependence on ligand choices and H-donors to exploit selectivity in products, however, yields were no more than

~50%. Additionally, homolysis studies with suitable complexes demonstrated the potential of this method for the formation of lactones, though, it is currently limited to β-hydrogen eliminated products and additional studies must be done to optimize for the reduced products. One pot reactions and catalytic reactions are currently unattainable through this ligand system either through external oxidants or enolate intermediates.

2.13 Experimental

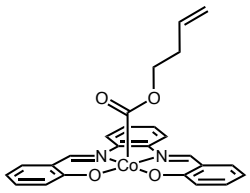
General Methods. All reactions were carried out in oven dried or flame dried glassware charged with a magnetic stir bar, were prepared under inert nitrogen atmosphere, and subsequently degassed with carbon monoxide. Solvents were dried by passage through columns of activated alumina. Anhydrous dichloroethane (DCE) was dried over 5 Å sieves to remove trace amounts of methanol. Commercially available alcohols were distilled from calcium hydride prior to use. Protected alcohols were synthesized by known literature procedures. Co(II)salen, Co(II)salph, Co(III)salen-OTs, Co(III)salen-I, Co(III)salen-Br(PPh_3) were prepared according to known literature procedures.

General procedures:

Procedure A: Oxidative carbonylation of salophen: To a mixture of Co(II) salophen (**2.4**) and potassium persulfate was added 12.5 mL DCE and the reaction mixture was purged with CO (balloon) for 10 s. The reaction mixture was then treated with the respective alcohol and stirred for 2 d, unless otherwise indicated, in the dark, at room temperature, under 1.0 atm CO. Reactions were tracked by TLC (3% MeOH in CH_2Cl_2) and a color change from brown to red was observed. Upon completion, the reaction mixture

was concentrated under reduced pressure. After re-dissolving in a minimal amount of CH_2Cl_2, reactions were precipitated from heptane and the suspension was filtered through Celite, then washed several times with heptane to remove excess unreacted alcohol. Subsequent washing with *i*-PrOH and CH_2Cl_2 separated the product from remaining Co(II) salophen. The red filtrate was concentrated to yield a red solid. No further purification was required.

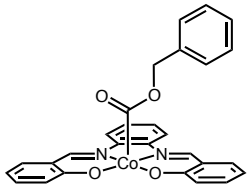
Procedure B: To a mixture of alkoxycarbonyl cobalt(III) salophen and TEMPO was added 1.5 mL of toluene and the reaction mixture was degassed by three cycles of freeze-pump-thaw. The reaction mixture was stirred for 4 h at room temperature and irradiated by green LEDs. Upon completion, the Co(II) product was precipitated by addition of heptane. Filtration of the suspension through Celite, washing several times with heptane, separated the TEMPO-trapped product and subsequent washing with CH_2Cl_2 isolated the Co(II) salophen. Concentration of the filtrates gave desired products with no further purification required.



3-Buten-1-yloxycarbonyl-cobalt salophen (2.5)

Prepared according to general procedure A using 93 mg **2.4** (0.25 mmol, 1.0 equiv), 110 μL 3-buten-1-ol (1.25 mmol, 5.0 equiv) and 270 mg potassium persulfate (1.0 mmol, 4.0 equiv). After 2 d, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (85 mg, 0.18 mmol, 72%). IR (film) 2951–3054, 1683, 1609, 1439, 1068 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.80 (s, 2H),

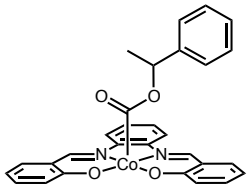
8.20 (dd, *J* = 5.9, *J* = 3.5 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.32 (dd, *J* = 6.1, *J* = 3.2 Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.55 (t, *J* = 7.4 Hz, 2H), 5.16–5.24 (m, 1H), 4.62–4.70 (m, 2H), 3.83 (t, *J* = 6.1 Hz, 2H), 1.68 (app q, *J* = 6.4 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.4 (C=O), 167.7, 156.6, 144.2, 135.1, 134.5, 134.1, 126.6, 122.1, 120.2, 116.2, 115.5, 113.5, 65.1, 33.0; HRMS (ESI) *m / z* calcd for $C_{25}H_{21}CoN_2O_4Na$ $(M + Na)^+$ 495.0726, found 495.0732.



Benzyloxycarbonyl-cobalt salophen (2.6)

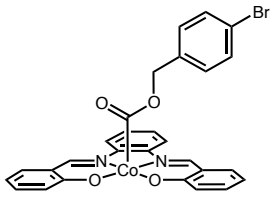
Prepared according to general procedure C using 93 mg **2.4** (0.25 mmol, 1.0 equiv), 130 μL benzyl alcohol (1.25 mmol, 5.0 equiv) and 270 mg potassium persulfate (1.0 mmol, 4.0 equiv). After 1 day, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (98 mg, 0.19 mmol, 77%). IR (film) 2852–3055, 1680, 1610, 1439, 1055 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.83 (s, 2H), 8.21 (dd, *J* = 6.1, *J* = 3.3 Hz, 2H), 7.52 (d, *J* = 7.1 Hz, 2H), 7.33 (dd, *J* = 5.7, *J* = 3.1 Hz, 2H), 7.27 (t, *J* = 7.4 Hz, 2H), 7.09 (t, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 4H), 6.66 (d, *J* = 7.4 Hz, 2H), 6.57 (t, *J* = 7.1 Hz, 2H), 4.92 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.1 (C=O), 167.8, 156.6, 144.2, 137.4, 135.2, 134.2, 127.7, 126.7, 126.6, 125.9, 122.2,

120.2, 115.6, 113.6, 66.7; HRMS (ESI) *m / z* calcd for $C_{28}H_{21}CoN_2O_4Na$ $(M + Na)^+$ 531.0726, found 531.0713.



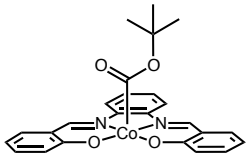
1-Phenethyloxycarbonyl-cobalt salophen (2.7)

Prepared according to the general salophen procedure A using 93 mg **2.4** (0.25 mmol, 1.0 equiv), 150 μL 1-phenylethanol (1.25 mmol, 5.0 equiv) and 270 mg potassium persulfate (1.0 mmol, 4.0 equiv). After 2 d, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (92 mg, 0.18 mmol, 72%). IR (film) 2924–3054, 1665, 1608, 1438, 1069 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.82 (s, 1H), 8.22 (dd, *J* = 10.3, *J* = 5.8 Hz, 2H), 7.55 (m, 2H), 7.32 (dd, *J* = 12.7, *J* = 6.7 Hz, 2H), 7.06 (t, *J* = 7.3 Hz, 1H), 6.99 (m, 4H), 6.69 (d, *J* = 7.4 Hz, 2H), 6.57 (dd, *J* = 11.5, *J* = 6.9 Hz, 2H), 5.69 (q, *J* = 6.5, 1H), 0.79 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.8, 156.6, 144.2, 143.0, 135.1, 134.1, 127.8, 126.6, 124.9, 122.2, 120.3, 115.4, 113.6, 72.7, 23.1; HRMS (ESI) *m / z* calcd for $C_{29}H_{23}CoN_2O_4Na$ $(M + Na)^+$ 545.0882, found 545.0875.



4-Bromobenzyloxycarbonyl-cobalt salophen (2.8)

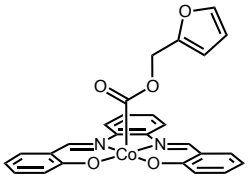
Prepared according to general procedure A using 93 mg **2.4** (0.25 mmol, 1.0 equiv), 230 mg 4-bromobenzyl alcohol (1.25 mmol, 5.0 equiv) and 270 mg potassium persulfate (1.0 mmol, 4.0 equiv). After 2 d, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (140 mg, 0.246 mmol, 98%). IR (film) 2958-3001, 1678, 1610, 1439, 1055 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.82 (s, 2H), 8.21 (dd, *J* = 6.2, *J* = 3.4 Hz, 2H), 7.53 (d, *J* = 6.9 Hz, 2H), 7.33 (dd, *J* = 6.2, *J* = 3.2 Hz, 2H), 7.28 (t, *J* = 6.9 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.65 – 6.55 (m, 2H), 4.88 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.2 (C=O), 167.7, 156.7, 144.2, 136.9, 135.2, 134.3, 130.6, 128.2, 126.7, 122.1, 120.1, 119.7, 115.6, 113.6, 66.0; HRMS (ESI) *m / z* calcd for $C_{28}H_{20}BrCoN_2O_4Na$ $(M + Na)^+$ 608.9831, found 608.9840.



***tert*-Butyloxycarbonyl-cobalt salophen (2.9)**

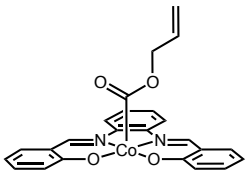
Prepared according to general procedure A using 93 mg **2.4** (0.25 mmol, 1.0 equiv), 120 μL *tert*-butanol (1.25 mmol, 5.0 equiv) and 270 mg potassium persulfate (1.0 mmol, 4.0 equiv). After 2 d, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (81 mg, 0.17 mmol, 67%). IR (film)

2975–3059, 1693, 1609, 1439, 1063 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.81 (s, 2H), 8.21 (app s, 2H), 7.52 (d, *J* = 7.5 Hz, 2H), 7.31 (app s, 2H), 7.24 (t, *J* = 7.5 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.54 (t, *J* = 7.1 Hz, 2H), 0.83 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.6, 167.7, 156.1, 144.2, 134.9, 133.8, 126.4, 122.0, 120.4, 115.2, 113.3, 80.6, 27.5; HRMS (ESI) *m / z* calcd for $C_{25}H_{23}CoN_2O_4Na$ $(M + Na)^+$ 497.0882, found 497.0885.



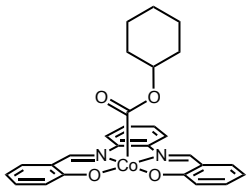
Furfuryloxycarbonyl-cobalt salophen (2.10)

Prepared according to general procedure A using 93 mg **2.4** (0.25 mmol, 1.0 equiv), 110 μL furfuryl alcohol (1.25 mmol, 5.0 equiv) and 270 mg potassium persulfate (1.0 mmol, 4.0 equiv). After 2 d, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (71 mg, 0.14 mmol, 57%). IR (film) 2924–3054, 1662, 1611, 1441, 1061 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.79 (s, 2H), 8.18 (app s, 2H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.31 (s, 3H), 7.24 (t, *J* = 7.5 Hz, 2H), 6.97 (d, *J* = 8.2 Hz, 2H), 6.54 (t, *J* = 7.5 Hz, 2H), 6.16 (s, 1H), 5.76 (s, 1H), 5.73 (s, 1H), 4.81 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.7, 156.6, 150.5, 144.1, 142.2, 135.1, 134.1, 126.6, 122.0, 120.1, 115.5, 113.5, 110.1, 107.9, 59.3; HRMS (ESI) *m / z* calcd for $C_{26}H_{19}CoN_2O_4Na$ $(M + Na)^+$ 521.0518, found 521.0516.



Allyloxycarbonyl-cobalt salophen (2.11)

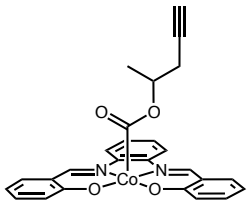
Prepared according to general procedure A using 93 mg **2.4** (0.25 mmol, 1.0 equiv), 85 μL allyl alcohol (1.25 mmol, 5.0 equiv) and 270 mg potassium persulfate (1 mmol, 4 equiv). After 2 d, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (93 mg, 0.20 mmol, 81%). IR (film) 2800–3100, 1665, 1610 1440, 1067 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.84 (s, 2H), 8.22 (dd, *J* = 6.3, *J* = 3.4 Hz, 2H), 7.54 (dd, *J* = 7.9, *J* = 1.5 Hz, 2H), 7.33 (dd, *J* = 6.2, *J* = 3.2 Hz, 2H), 7.28–7.22 (m, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.56 (t, *J* = 7.3 Hz, 2H), 5.31–5.38 (m, 1H), 4.72 (dd, *J* = 10.8, *J* = 1.8 Hz, 1H), 4.58 (dd, *J* = 17.3, *J* = 1.9 Hz, 1H), 4.38 – 4.33 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.8, 156.6, 144.2, 135.1, 134.2, 133.3, 126.6, 122.1, 120.1, 115.5, 113.5, 65.5; HRMS (ESI) *m / z* calcd for $C_{25}H_{21}CoN_2O_4Na$ $(M + Na)^+$ 481.0569, found 481.0557.



Cyclohexyloxycarbonyl-cobalt salophen (2.12)

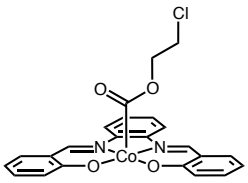
Prepared according to general procedure A using 93 mg **2.4** (0.25 mmol, 1.0 equiv), 130 μL cyclohexanol (1.25 mmol, 5.0 equiv) and 270 mg potassium persulfate (1.0 mmol, 4.0 equiv). After 2 d the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (77 mg, 0.15 mmol, 62%). IR (film)

2934, 1688, 1609, 1461, 1072 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.83 (s, 2H), 8.21 (dd, *J* = 6.1, *J* = 3.2 Hz, 2H), 7.53 (d, *J* = 7.6 Hz, 2H), 7.31 (dd, *J* = 6.1, *J* = 3.2 Hz, 2H), 7.23 (t, *J* = 7.6 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.54 (t, *J* = 7.2 Hz, 2H), 4.70 (m, 1H), 0.90–1.15 (m, 10H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.8, 156.3, 144.2, 135.0, 134.0, 126.5, 122.0, 120.4, 115.3, 113.4, 72.4, 30.6, 25.0, 21.1; HRMS (ESI) *m / z* calcd for $C_{27}H_{25}CoN_2O_4$ $(M + Na)^+$ 523.1039, found 523.1038.



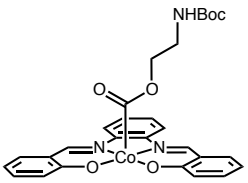
4-Pentynyl-2-oxycarbonyl-cobalt salophen (2.13)

Prepared according to general procedure A using 93 mg **2.4** (0.25 mmol, 1.0 equiv), 120 μL 4-pentyn-2-ol (1.25 mmol, 5.0 equiv) and 270 mg potassium persulfate (1.0 mmol, 4.0 equiv). After 2 d, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (81 mg, 0.17 mmol, 66%). IR (film) 3287, 3014–3054, 1679, 1609, 1439, 1075 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.79 (d, *J* = 5.0 Hz, 2H), 8.19 (app s, 2H), 7.52 (d, *J* = 7.6 Hz, 2H), 7.31 (dd, *J* = 5.6, *J* = 2.9 Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 2H), 6.98 (d, *J* = 6.6 Hz, 2H), 6.55 (t, *J* = 7.2 Hz, 2H), 4.74 – 4.66 (m, 1H), 2.50* (s, 1H), 1.75 (m, 2H), 0.65 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.7, 156.5, 144.1, 135.0, 134.0, 126.5, 122.0, 120.3, 115.4, 113.4, 79.7, 72.3, 69.2, 24.8, 18.7; HRMS (ESI) *m / z* calcd for $C_{26}H_{21}CoN_2O_4Na$ $(M + Na)^+$ 507.0726, found 507.0731. *Terminal alkyne peak obscured by DMSO peak was observed by COSY.



2-Chloroethoxycarbonyl-cobalt salophen (2.14)

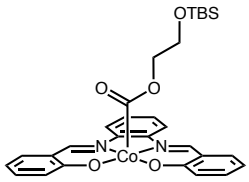
Prepared according to general procedure A using 93 mg **2.4** (0.25 mmol, 1.0 equiv), 84 μL 2-chloroethanol (1.25 mmol, 5.0 equiv) and 270 mg potassium persulfate (1.0 mmol, 4.0 equiv). After 2 d, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (67 mg, 0.14 mmol, 56%). IR (film) 2923–3053, 1682, 1610, 1440, 1057 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.82 (s, 2H), 8.21 (dd, *J* = 5.5, *J* = 3.1 Hz, 2H), 7.53 (d, *J* = 7.7 Hz, 2H), 7.32 (dd, *J* = 5.8, *J* = 2.9 Hz, 2H), 7.25 (t, *J* = 7.7 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.55 (t, *J* = 7.1 Hz, 2H), 4.02 (t, *J* = 5.2 Hz, 2H), 3.08 (t, *J* = 5.2 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.7, 156.7, 144.2, 135.1, 134.2, 126.6, 122.0, 120.2, 115.5, 113.5, 65.1, 42.7; HRMS (ESI) *m / z* calcd for $C_{23}H_{18}ClCoN_2O_4Na$ $(M + Na)^+$ 503.0179, found 503.0170.



Boc-2-aminoethoxycarbonyl-cobalt salophen (2.15)

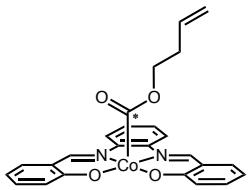
Prepared according to general procedure A using 93 mg **2.4** (0.25 mmol, 1.0 equiv), 202 mg *tert*-butyl (2-hyroxyethyl) carbamate (1.25 mmol, 5.0 equiv) and 270 mg potassium persulfate (1.0 mmol, 4.0 equiv). After 2 d, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (110 mg, 0.20 mmol, 80%). IR (film) 2930–2980, 1682, 1611, 1441, 1067 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6)

δ 8.82 (s, 2H), 8.21 (dd, *J* = 6.3, *J* = 3.3 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.32 (dd, *J* = 6.2, *J* = 3.2 Hz, 2H), 7.25 (t, *J* = 7.7 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.56 (t, *J* = 7.3 Hz, 2H), 5.66 (s, 1H), 3.72 (t, *J* = 6.7 Hz, 2H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.7, 156.6, 155.1, 144.1, 135.1, 134.3, 126.6, 122.0, 120.2, 115.5, 113.6, 77.8, 63.9, 28.1; HRMS (ESI) *m / z* calcd for $C_{28}H_{28}CoN_3O_6Na$ $(M + Na)^+$ 584.1202, found 584.1206.



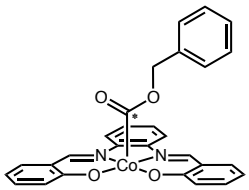
2-((*tert*-butyldimethylsilyl)oxy)ethoxycarbonyl-cobalt salophen (2.16)

Prepared according to general procedure A using 93 mg **2.4** (0.25 mmol, 1.0 equiv), 220 mg 2-((*tert*-butyldimethylsilyl)oxy)ethanol (1.25 mmol, 5.0 equiv) and 270 mg potassium persulfate (1.0 mmol, 4.0 equiv). After 2 d, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (130 mg, 0.23 mmol, 90%). IR (film) 2856–2954, 1672, 1612, 1441, 1078 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.79 (s, 2H), 8.19 (dd, *J* = 6.1, *J* = 3.3 Hz, 2H), 7.52 (d, *J* = 7.7 Hz, 2H), 7.31 (dd, *J* = 6.1, *J* = 3.1 Hz, 2H), 7.24 (t, *J* = 7.7 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 6.54 (t, *J* = 7.2 Hz, 2H), 3.82 (t, *J* = 5.7 Hz, 2H), 3.07 (t, *J* = 5.7 Hz, 2H), 0.70 (s, 9H), –0.19 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.7, 156.6, 144.2, 135.1, 134.1, 126.6, 122.0, 120.2, 115.5, 113.4, 66.7, 60.8, 25.7, 17.8, 5.6; HRMS (ESI) *m / z* calcd for $C_{29}H_{33}CoN_2O_5SiNa$ $(M + Na)^+$ 599.1383, found 599.1371.



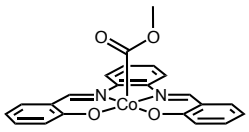
^{13}C-3-buten-1-yloxycarbonyl-cobalt salophen (2.5*)

To a mixture of 93 mg **2.4** (0.25 mmol, 1.0 equiv), 110 μL 3-buten-1-ol (1.25 mmol, 5.0 equiv) and 270 mg potassium persulfate (1.0 mmol, 4.0 equiv) was added 13 mL DCE and the reaction mixture was purged with ^{13}CO (balloon) for 10 s. The reaction mixture was stirred for 2 d in the dark, at room temperature, under 1.0 atm ^{13}CO. The reaction was tracked by TLC (3% MeOH in DCM). Upon completion, the reaction mixture was concentrated under reduced pressure. After re-dissolving in a minimal amount of CH_2Cl_2, reactions were precipitated from heptane and the suspension was filtered through Celite, then washed several times with heptane to remove excess unreacted alcohol. Subsequent washing with *i*-PrOH and CH_2Cl_2 separated the product from remaining Co(II) salophen. The red filtrate was concentrated to yield a red crystalline solid (86 mg, 0.18 mmol, 73%). IR (film) 2940-3035, 1613, 1430, 1042 cm^{-1};^{1}H NMR (500 MHz, DMSO-d_6) δ 8.85 (s, 2H), 8.22 (s, 2H), 7.55 (d, J = 7.8 Hz, 2H), 7.31 (dd, J = 6.0 Hz 2H), 7.25 (d, J = 7.7 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.56 (t, J = 7.1 Hz, 2H), 5.15–5.22 (m, 1H), 4.63–4.68 (m, 2H), 3.85 (t, J = 6.1 Hz, 2H), 1.69 (q, J = 6.6 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.5, 159.5, 156.3, 144.0, 134.9, 134.3, 133.9, 126.4, 121.8, 119.9, 115.9, 115.2, 113.3, 64.9, 32.8. HRMS (ESI) *m / z* calcd for $C_{24}(^{13}C)H_{21}CoN_2O_4Na$ $(M + Na)^+$ 496.0765, found 496.07361.



^{13}C-Benzyloxycarbonyl-cobalt salophen (2.6*)

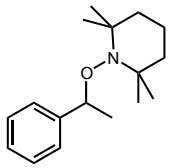
To a mixture of 25 mg **2.4** (0.07 mmol, 1 equiv), 200 mg oxone® (0.32 mmol, 5.0 equiv) and 33 μL benzyl alcohol (0.32 mmol, 5.0 equiv) was added 1.4 mL DCE and the reaction mixture was purged with ^{13}CO (balloon) for 10 s. The reaction mixture was stirred for 17 h in the dark, at room temperature, under 1 atm ^{13}CO. The reaction was tracked by TLC (3% MeOH in DCM). Upon completion, the reaction mixture was loaded onto a silica column and eluted with 3% MeOH in CH_2Cl_2 and the red fractions were collected. Concentration afforded a red crystalline solid (18 mg, 0.035 mmol, 50%). IR (film) 2922–3057, 1611, 1580, 1440, 1040; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.83 (s, 2H), 8.21 (dd, *J* = 6.1, *J* = 3.3 Hz, 2H), 7.52 (d, *J* = 7.9 Hz, 2H), 7.33 (dd, *J* = 6.2, *J* = 3.2 Hz, 2H), 7.26 (dt, *J* = 13.4, *J* 9.2 Hz, 2H), 7.09 (t, *J* = 7.0 Hz, 1H), 7.00 (t, *J* = 7.9 Hz, 4H), 6.66 (d, *J* = 8.0 Hz, 2H), 6.56 (dd, *J* = 14.5, *J* = 7.6 Hz, 2H), 4.91 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.1 (C=O), 167.8, 156.6, 144.2, 137.4, 135.2, 134.2, 127.7, 126.7, 125.9, 122.1, 120.1, 115.6, 113.6, 66.7; HRMS (ESI) *m / z* calcd for $C_{27}(^{13}C)H_{21}CoN_2O_4Na$ $(M + Na)^+$ 532.0760, found 532.0761.



Methoxycarbonyl-cobalt salophen (2.17)

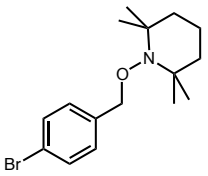
To a mixture of 46 mg **2.4** (0.1 mmol, 1.0 equiv) and 9.5 mg *p*-toluenesulfonic acid monohydrate (0.05 mmol, 0.50 equiv) in 10 mL DCE was added 20 μL MeOH (0.50 mmol,

5.0 equiv). The reaction was stirred for 3 h then concentrated and purified via column chromatography (silica, 3% MeOH:CH_2Cl_2) affording a red crystalline solid (31 mg, 0.07 mmol, 70%). IR (film) 2920, 1665, 1609, 1580, 1438, 1048 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.82 (s, 2H), 8.21 (dd, J = 6.1, J = 3.4 Hz, 2H), 7.54 (d, J = 7.0 Hz, 2H), 7.32 (dd, J = 6.1, J = 3.2 Hz, 2H), 7.25 (t, J = 7.6, 2H), 6.98 (d, J = 8.5 Hz, 2H), 6.56 (t, J = 7.2 Hz, 2H), 3.34 (s, 3H).^{13}C NMR (125 MHz, DMSO-d_6) δ 167.8, 156.7, 144.2, 135.2, 134.2, 126.7, 122.1, 120.1, 155.6, 113.6, 53.7; HRMS (ESI) *m / z* calcd for $C_{22}H_{17}CoN_2O_4Na$ $(M + Na)^+$ 455.0413 found 455.0412.



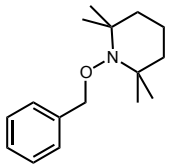
2,2,6,6-tetramethyl-1-(1-phenylethoxy)piperidine (2.20)

Prepared according to the general procedure B using 19 mg **2.7** (0.02 mmol, 1.0 equiv.) and 6.2 mg TEMPO (0.04 mmol, 2.0 equiv.). After 4 h, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a clear oil (4.0 mg, 0.016 mmol, 80%). IR (film) 2924, 2136, 1966, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 4H), 7.22 (m, 1H), 4.78 (q, J = 6.7 Hz, 1H), 1.48 (d, J = 6.7 Hz, 3H), 1.21 (m, 18H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 128.1, 127.3, 101.5, 59.9, 59.3, 39.6, 32.9, 29.5, 20.1, 17.0, 0.85. HRMS (ESI) *m / z* calcd for $C_{17}H_{28}NO$ $(M + H)^+$ 262.2165, found 262.2164.



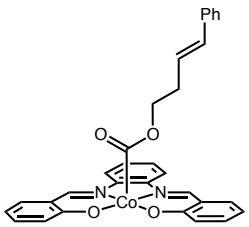
1-((4-bromobenzyl)oxy)-2,2,6,6-tetramethylpiperidine (2.21)

Prepared according to the general procedure B using 21 mg **2.8** (0.02 mmol, 1.0 equiv.), 6.2 mg TEMPO (0.04 mmol, 2.0 equiv.). After 4 h, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a clear oil (4.8 mg, 0.015 mmol, 74%). IR (film) 2928, 1508, 1264, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 4.69 (s, 2H), 1.17 (d, *J* = 12.6 Hz, 12H), 1.07 (s, 6H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 131.3, 129.1, 121.2, 78.0, 60.0, 39.7, 33.1, 29.7, 20.3, 17.1); HRMS (ESI) *m / z* calcd for $C_{16}H_{25}BrNO$ $(M + H)^+$ 326.1120, found 326.1118.



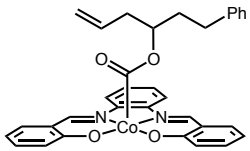
1-(benzyloxy)-2,2,6,6-tetramethylpiperidine (2.22)

Prepared according to the general procedure B using 16 mg **2.6** (0.02 mmol, 1.0 equiv.), 6.2 mg TEMPO (0.04 mmol, 2 equiv.). After 4 h, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a clear oil (4.8 mg, 0.015 mmol, 74%). IR (film) 2940, 1514, 1240, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 4H), 7.21 (m, 1H), 4.83 (s, 2H), 1.17–1.09 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 130.7, 128.2, 105.9, 59.9, 58.8, 39.5, 32.4, 29.1, 19.9, 17.1; HRMS (ESI) *m / z* calcd for $C_{16}H_{26}NO$ $(M + H)^+$ 248.2014, found 248.2013



(*E*)-4-phenylbut-3-en-1-oxycarbonyl-cobalt salophen (2.31)

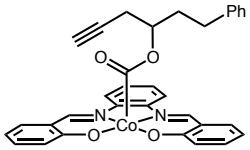
Prepared according to general procedure A using 25 mg **2.4** (0.07 mmol, 1.0 equiv), 52 mg (*E*)-4-phenylbut-3-en-1-ol (0.40 mmol, 5.0 equiv) and 76 mg potassium persulfate (0.30 mmol, 4.0 equiv). After 2 d, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (38 mg, 0.60 mmol, 82%)^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 2H), 8.20 (app s, 2H), 7.55 (d, J = 7.7 Hz, 2H), 7.30 (m, 7H), 7.01 (t, J = 7.6 Hz, 2H), 6.59 (d, J = 8.0 Hz, 2H), 6.14 (t, J = 8.1 Hz, 2H), 5.65.8 (m, 2H), 3.94 (s, 2H), 1.89 (s, 2H).



1-phenylhex-5-en-3-oxycarobnyl-cobalt salophen (2.34)

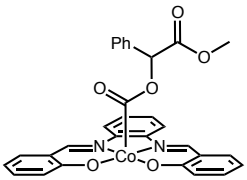
Prepared according to general procedure A using 93 mg **2.4** (0.25 mmol, 1.0 equiv), 180 μL 1-phenylhex-5-en-3-ol (1.0 mmol, 4.0 equiv) and 270 mg potassium persulfate (1.0 mmol, 4.0 equiv). After 2 d, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (96 mg, 0.17 mmol, 67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (s, 2H), 8.00 (s, 2H), 7.56 (d, J = 7.5 Hz, 2H) 7.30 – 7.28 (m, 5H), 7.18 – 7.06 (m, 4H), 6.96 – 6.89 (m, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.45 – 6.40 (m,

2H), 5.50 – 5.35 (m, 1H), 4.90 (d, J = 9.0 Hz, 1H), 2.30 – 2.10 (m, 2H), 1.94 (m, 2H), 1.48 – 1.21 (m, 2H).



1-phenylhex-5-yn-3-oxycarbonyl-cobalt salophen (2.38)

Prepared according to general procedure A using 93 mg **2.4** (0.25 mmol, 1.0 equiv), 170 μL 1-phenylhex-5-yn-3-ol (1.0 mmol, 4.0 equiv) and 270 mg potassium persulfate (1.0 mmol, 4.0 equiv). After 2 d, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (91 mg, 0.16 mmol, 63%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 2H), 8.24 – 8.13 (m, 2H), 7.51 (d, J = 8.1 Hz, 2H), 7.34 – 7.13 (m, 9H), 6.96 (d, J = 8.6 Hz, 2H), 6.53 (t, J = 7.4 Hz, 2H), 4.85 (m, 1H), 2.54 (m, 1H), 2.35 – 1.34 (m, 2H), 0.85 (t, J = 7.5 Hz, 2H), 0.50 (dt, J = 7.4, 4.7 Hz, 2H).



((2-methoxy-2-oxo-1-phenylethoxy)carbonyl)cobalt salophen (2.45)

Prepared according to general procedure A using 56 mg **2.4** (0.15 mmol, 1.0 equiv), 120 mg methyl 2-hydroxy-2-phenylacetate (0.8 mmol, 5.0 equiv) and 200 mg potassium persulfate (0.8 mmol, 5.0 equiv). After 2 d, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (38 mg, 0.60 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 2H), 8.09 – 7.97 (m, 2H), 7.62 – 7.22 (m, 14H), 6.81 (t, J = 7.5 Hz, 2H), 5.12 (s, 1H), 3.63 (s, 3H).

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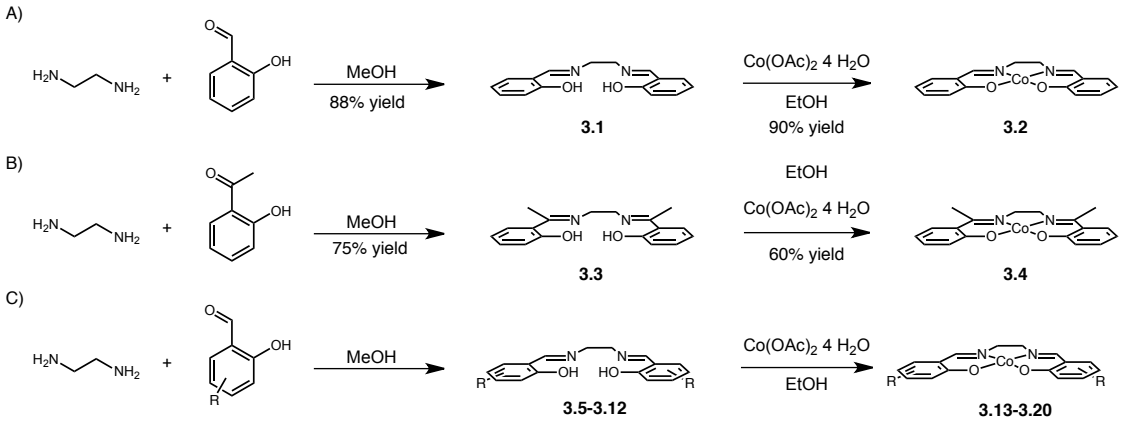
Chapter 3 : Synthesis and Irradiation of Alkoxycarbonyl Cobalt(III) Salen Complexes

3.1 Introduction

Pattenden and co-workers established notable parallels between acyl/alkoxycarbonyl cobalt(III) salen complexes and their alkyl counterparts as part of their pioneering studies on the synthetic utility and reactivity of organocobalt species as radical precursors.[1–3] However, alkoxycarbonyl cobalt complexes have been studied much less than corresponding alkyl complexes and their radical chemistry, in part due to a lack of detailed investigations into the synthesis and properties of this class of organocobalt(III) complexes.[4–7] One limitation of these acyl and alkoxycarbonyl cobalt species is the synthesis typically requires reduction to a Co(I) anionic species using strong reductants such as Na/Hg amalgam and the use of acyl chloride reagents.[3] Seminal work by Costa and Mestroni in the 1960s reported a synthesis of these alkoxycarbonyl cobalt complexes with Co-salen using both the traditional reduction method as well as directly from alcohols.[8,9] A number of simple alkoxy substituents were incorporated under a carbon monoxide atmosphere in alcohol solvent (MeOH, EtOH, iPrOH); however, no yields were reported. Herein we describe the synthesis of alkoxycarbonyl Co(III) salen complexes from a range of alcohols, full characterization of the compounds formed, and radical generation studies.

3.2 Synthesis of Cobalt(II) Salen and Co(III) Salen

All salen complexes were prepared as previously reported.[10–13] Condensation of ethylenediamine with 2-hydroxybenzaldehyde (Table 3.1, A), 2-acetophenol (Table 3.1, B) or substituted 2-hydroxybenzaldehydes (Table 3.1, C) yielded salen ligands in excellent yields. Incorporation of cobalt into the ligand was achieved by refluxing cobalt acetate tetrahydrate with the respective ligand and proceeded smoothly in all ligands,[14–16] with some difficulty forming complex **3.4** due to the air sensitivity of the complex. Recrystallization under nitrogen improved the yields significantly, and once compound **3.4** was isolated, it was bench stable for months.



R	Yield **3.5-3.12**	Yield **3.13-3.20**
5-Methyl	**3.5**, 95%	**3.13,** 77%
5-Methoxy	**3.6,** 81%	**3.14,** 77%
5-Nitro	**3.7,** 95%	**3.15,** 81%
5-Chloro	**3.8,** 96%	**3.16,** 91%
Naphthyl	**3.9,** 54%	**3.17,** 87%
3-Methoxy	**3.10,** 90%	**3.18,** 77%
5-Bromo	**3.11,** 93%	**3.19,** 92%
3,5-ditertbutyl	**3.12,** 93%	**3.20,** 89%

Table 3.1 Synthesis of cobalt salen ligands

Numerous salen ligands were synthesized to test the effects of electronics on our proposed reactions. Additionally, oxidation of the Co(II)salen derivatives was performed

according to literature procedures (Figure 3.1).[8,17–19] Reactions with Co(II) salen and iodine or *p*-toluenesulfonic acid are performed under air to achieve oxidation and products were easily isolable by filtration.

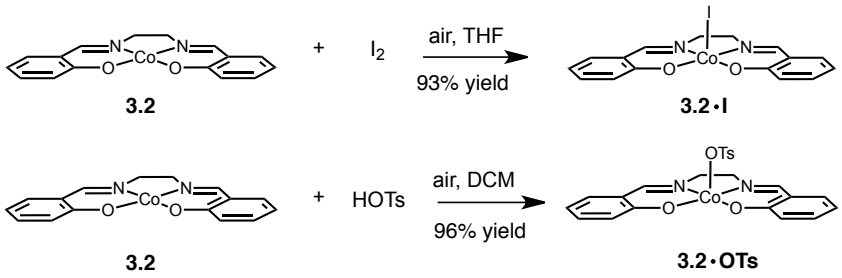
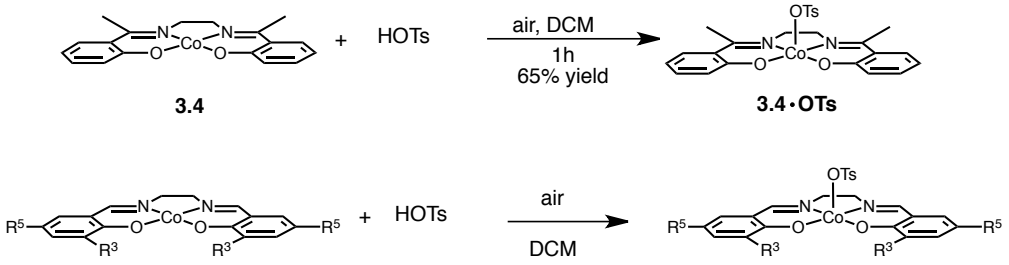


Figure 3.1 Synthesis of Co(III)salen complexes

Based on early successes by fellow graduate student Raymond Sullivan with carbonylation experiments using salen•OTs over the other Co(III) salen compounds, Co(III)salen tosylate derivatives were synthesized for the various substituted salen complexes (Table 3.2). Synthesis of all tosylate products was achieved in excellent yields (81%–94%) and pure product was easily isolated by precipitation out of the reaction mixture by addition of hexanes and filtration. With these compounds in hand, we have a



R	Yield
NO_2	**3.15•OTs**, 81%
Cl	**3.16•OTs**, 92%
Br	**3.19•OTs**, 88%
5-Me	**3.13•OTs,** 85%
5-OMe	**3.14•OTs**, 81%
3-OMe	**3.18•OTs**, 94%

Table 3.2 Oxidation of Co(II)salen derivatives to Co(III)salen-OTs

variety of electron rich and electron-withdrawn salen ligands to test with our carbonylation protocol.

3.3 Redox-Neutral Synthesis of Alkoxycarbonyl Salen Complexes

Initial studies on the formation of alkoxycarbonyl salen complexes via the methods of Costa and Mestrioni[9] was initially optimized by Raymond Sullivan. Cobalt(III)salen complexes were treated with simple alcohols and 1 atm of CO to yield the alkoxycarbonyl cobalt(III) complex (Table 3.3, row 1).

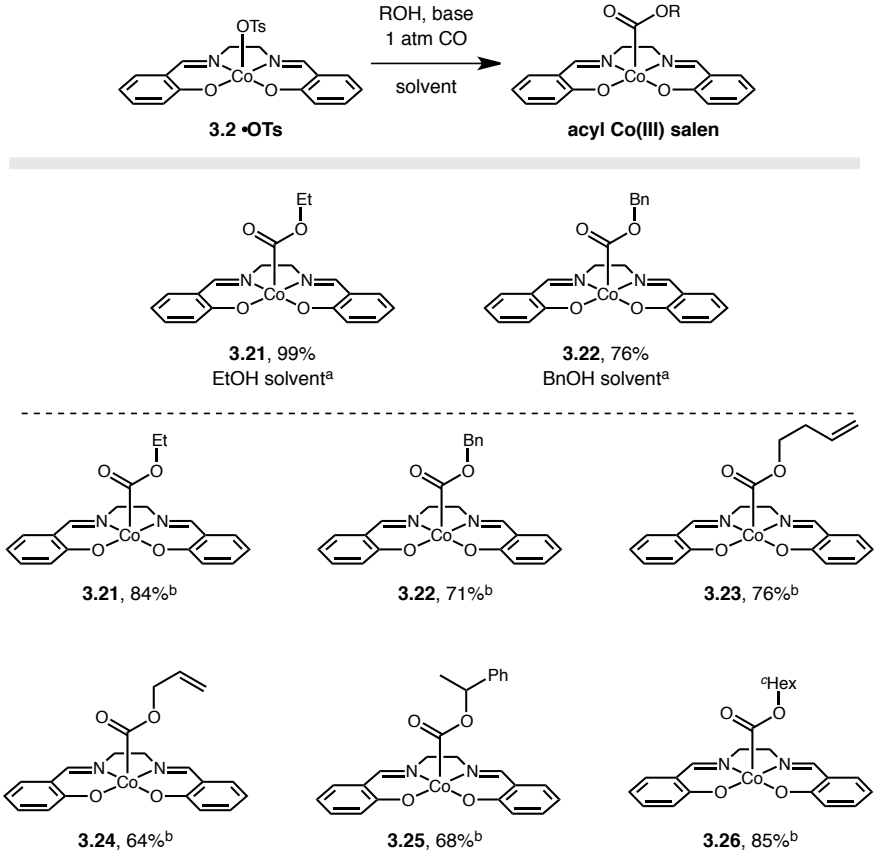
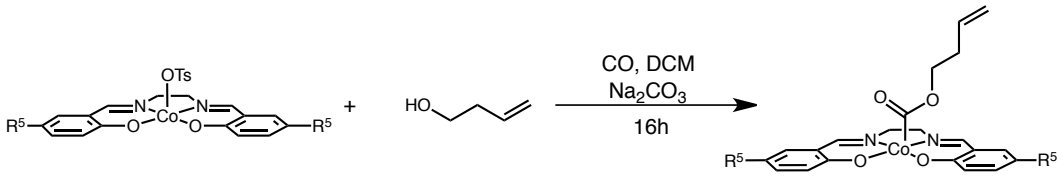


Table 3.3 Redox-neutral synthesis of alkoxycarbonyl Co(III)salen complexes. [a]Reaction conditions: Co(salen)OTs (0.1 mmol), sodium alkoxide (1.0 mmol), solvent (4.5 mL), 1 atm CO, rt. [b]Co(salen)OTs (0.2 mmol), alcohol (1.0 mmol), Na_2CO_3 (0.6 mmol), CH_2Cl_2 (8 mL), 1 atm CO, rt.

These reactions were found to be improved by the addition of an alkoxide base (1M) in alcohol and the product could be isolated as the red solid by precipitation with heptane. Alkoxide bases could be made via the addition of sodium hydride or sodium metal in the alcohol. However, this method is limited due to the use of the alcohol as the solvent, limiting our scope to abundant, low boiling alcohols. As such, we set out to improve this process and found that the inorganic bases could be utilized instead of the alkoxide derivatives, making the setup of these reactions much simpler. Through base and solvent evaluation, Raymond accomplished the same transformations as previously reported, reducing the required alcohol to 5 equivalents. Inorganic bases such as Na_2CO_3 and Na_3PO_4 and solvents such as CH_2Cl_2 and toluene maintained the good yields (71-84%) and the product could be isolated with an aqueous workup. These salen complexes were not stable to silica gel or alumina chromatography and could only be purified by recrystallization.

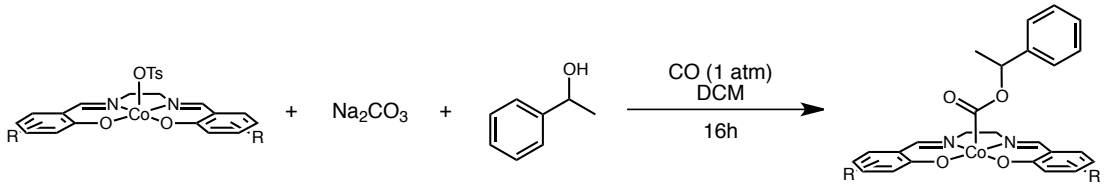
With these new conditions in hand we set out to assess the scope of alcohols that could be incorporated. Starting from **3.2•OTs** a variety of 1º and 2º alkyl and aryl alcohols were tested. Under the optimized conditions, 3 equiv Na_2CO_3 and 5 equiv alcohol, these alcohols were incorporated into the requisite complexes in good to excellent yields (64-85%). With Raymond's success at redox-neutral carbonylation from **3.2•OTs**, I investigated similar carbonylation using the derivatized salen ligands (Table 3.4). Carbonylation to form the butenol alkoxycarbonyl complexes **3.27-3.29** was performed under optimized conditions.



R	Yield
5-OMe	**3.27**, 70%
–	**3.23**, 61%
5-Me	**3.28**, 0%
5-NO_2	**3.29**, 0%

Table 3.4 Redox-neutral carbonylation of Co(III)salen-OTs derivatives

Synthesis of the unsubstituted product **3.23** acted as a control experiment for comparison, and formation of butenyloxycarbonyl product **3.27** was achieved in good yield, however formation of **3.28** and **3.29** were unsuccessful.



R	Yield
3-OMe	**3.30**, 71%
5-OMe	**3.31**, 70%
5-Me	**3.32**, 52%
5-Br	**3.33**, 23%[b]
5-Cl	**3.34**, 74%[b]
5-NO_2	**3.35**, 0%

Table 3.5 Redox-neutral carbonylation of salen derivatives with 1-phenylethanol. [b]Reaction run at 2 atm CO

These conditions were also tested to synthesize 1-phenethyl-alkoxycarbonyl Co(III)salen derivatives (Table 3.5). Carbonylation was achieved in moderate to good yields for the salen ligands containing strongly electron-donating groups such as methyl (**3.32**) or methoxy (**3.30** and **3.31)**. When electron-withdrawing groups were employed, such as bromide, a sharp decrease in yield was observed and strongly withdrawing group

such as nitro fully inhibited carbonylation reactions. It was only when carbon monoxide pressure was increased from balloon pressure to 2 atm did carbonylation of more challenging derivates proceed (5-chloro derivative **3.34**), however, **3.35** was never formed even under our forcing conditions.

3.4 In-situ Oxidation/Carbonylation of Cobalt Salen

While optimizing our redox-neutral carbonylation, Peng, Fu and coworkers reported a one-step oxidation/carbonylation from Co(II)salen.[20] They achieved the formation of a methoxycarbonyl-Co(III)salen using their method and methanol as a co-solvent with toluene. From optimization studies (see Chapter 2) we explored the in-situ oxidation carbonylation with Co(II)salen (Table 3.6).

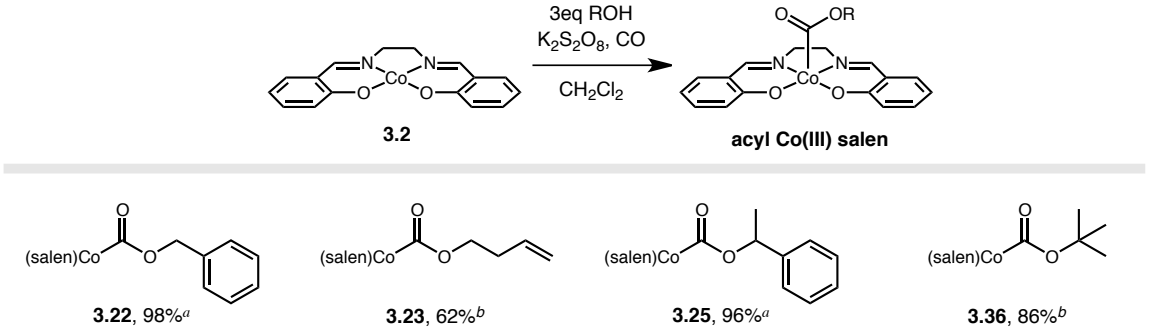
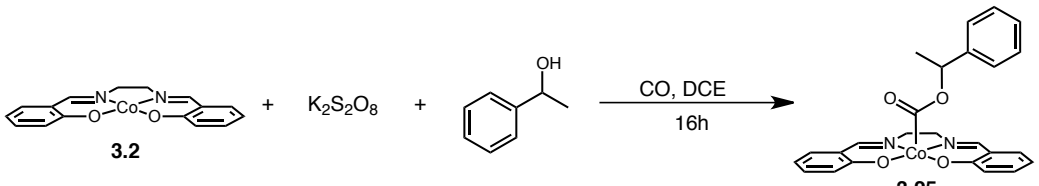


Table 3.6 In-situ oxidation-carbonylation of Co(II)salen. [a]Reaction conditions: Co(salen) (0.154 mmol), alcohol (0.462 mmol), $K_2S_2O_8$ (0.462 mmol), CH_2Cl_2 (7.5 mL), 1 atm CO, rt. [b]Reaction conditions: Co(salen) (0.3 mmol), alcohol (0.9 mmol), $K_2S_2O_8$ (0.9 mmol), CH_2Cl_2 (15 mL), 1 atm CO, rt

Carbonylation was efficiently achieved with 1º, 2º, and 3º alcohols under the standard conditions. The *in-situ* oxidation-carbonylation method allowed access to alkoxycarbonyl complex **3.36** which was previously unattained by the redox-neutral conditions. Additionally, increased yields were obtained for **3.22** and **3.25** with this

method. Interestingly, excellent yields of the alkoxycarbonyl complexes could be achieved with lower equivalents of alcohol than the corresponding salophen complexes. This is surprising due to the similarities in redox potentials of salen and salophen (⁻0.23V $Co^{II/III}$Salen vs ⁻0.19V $Co^{II/III}$Salophen, vs. SCE reference).[21,22]

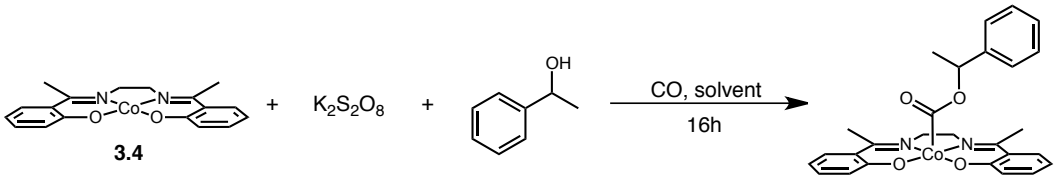


Atmosphere	$K_2S_2O_8$	Yield
CO	3 equiv	72%
CO	–	0%
CO + air	–	trace

Table 3.7 Oxidation-carbonylation of 3.2 under different oxidative conditions

Control experiments were run to determine if potassium persulfate was required for oxidation or if air would be sufficient.[12] Carbonylation reactions were run in the presence and absence of $K_2S_2O_8$ with either CO or a mixture of CO and air (Table 3.7). The atmosphere of the reactions was introduced by bubbling either CO or CO and air through the solvent using a balloon. As expected, the reaction with oxidant and CO gave good conversion to product and the reaction with no oxidant resulted in only starting material. The reaction with air as an oxidant generated only trace amounts of **3.25**, indicating that air alone is not a sufficient oxidant for this transformation. The oxidative carbonylation process was also applied to the more electron-rich 7,7'-dimethylsalen complex **3.4**, giving the corresponding alkoxycarbonyl product **3.37** (Table 3.8). Initial studies (Table 3.8, A) showed a similar trend of reactivity based on solvent as other salen ligands, however, carbonylation was optimal in DCM instead of the standard conditions

with DCE. Furthermore, this ligand system is significantly easier to oxidize than its unsubstituted counterpart and 2 equivalents of $K_2S_2O_8$ is sufficient to oxidize **3.4** as opposed to the 4 equivalents for **3.2**. Although found to be successful for oxidation/carbonylation of **3.4**, this oxidative carbonylation method was ineffective with the other substituted salen derivatives, giving no desired alkoxycarbonyl complex.



(A)

Solvent	Yield
DCM	64%
DCE	50%
THF	44%
CH_3CN	9%

(B)

$K_2S_2O_8$ equiv	Yield
1	53%
2	70%
3	71%
4	74%

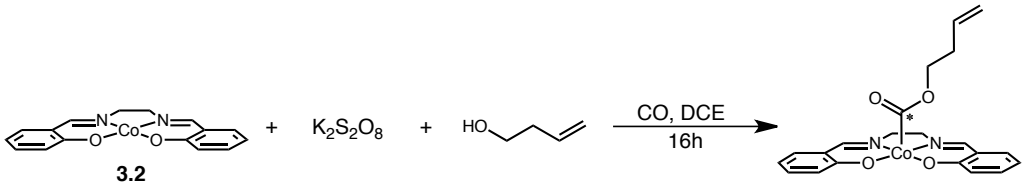
Table 3.8 In-situ oxidation-carbonylation of 7,7'-dimethyl salen **3.4**

3.5 NMR Studies

As few alkoxycarbonyl cobalt(III)salen complexes have previously been made, there is a lack of characterization data available, and even when compounds were made, even fewer were properly characterized. As such, in our synthesis studies we took an interest in fully characterizing and understanding these alkoxycarbonyl complexes. These cobalt salen derivatives were often quite insoluble and if any trace of Co(II)salen was present in the ^{1}H NMR, the signal from the Co(III) complexes were compromised. The diamagnetic Co(III) complexes are symmetrical in solution by NMR, potentially indicating facile rotation about the Co–C bond. The α-oxy C–H's show distinct resonances in the ^{1}H NMR spectrum at 3.39–5.83 ppm, while in most cases the β-oxy C–H's were shifted

upfield due to their proximity to the extended aromatic ligand framework (e.g. **3.21:** α-oxy C–H, 3.96 ppm and β-oxy C–H, 0.69 ppm.

Analysis by carbon NMR was also performed and all the alkyl and aryl resonances could be identified, however, the carbonyl carbon was difficult to identify or even fully



CO	Yield
^{12}CO	62%
^{13}CO	44%

Table 3.9 Carbonylation of **3.2** with ^{13}C labeled carbon monoxide

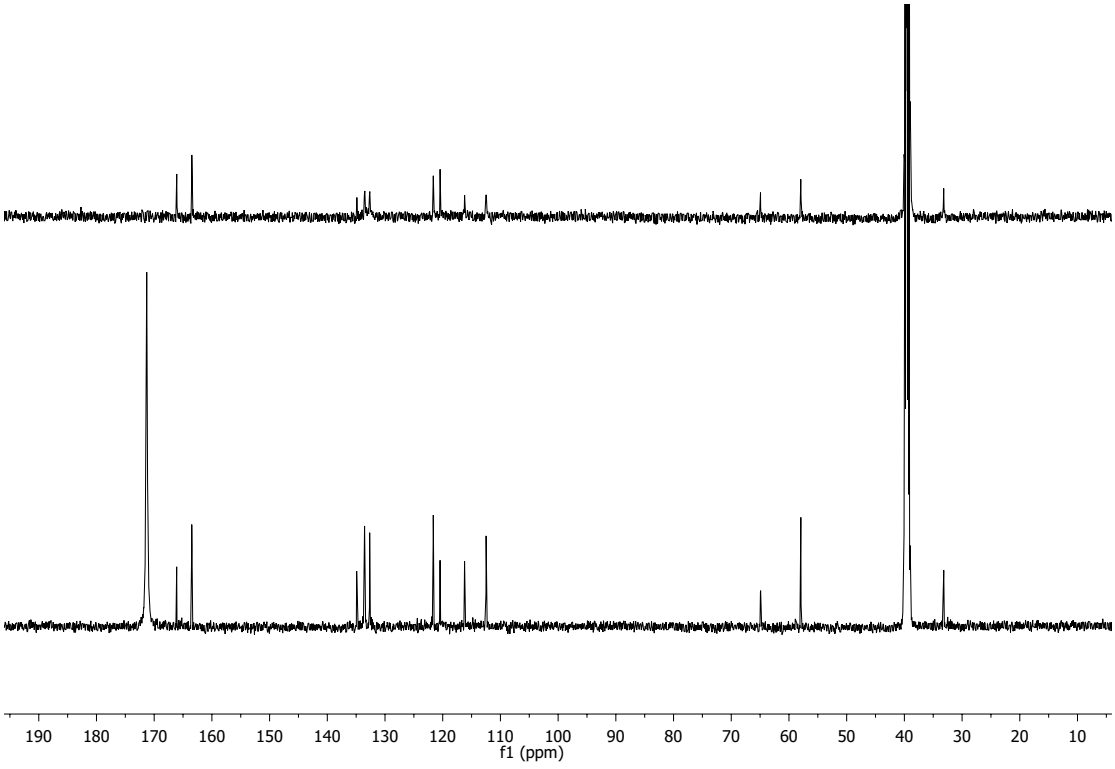
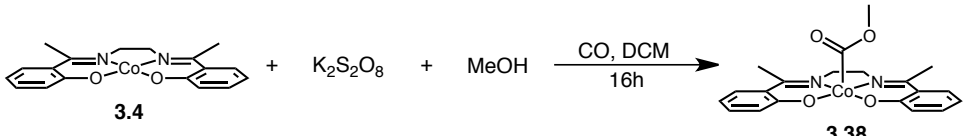


Figure 3.2 ^{13}C NMR of unlabeled **3.23** and labeled **3.23***

absent in the ^{13}C NMR spectrum, depending on solubility of the compound. As many of these complexes have low solubility it was often difficult to identify that resonance. To address this issue, labeling studies were performed with ^{13}C-labeled carbon monoxide (Table 3.9). Carbonylation with ^{13}C carbon monoxide did coincide with a moderate drop in yield, indicating that carbonylation may be involved in the rate determining step. However, further mechanistic studies would have to be pursued to confirm this speculation. When comparing the ^{13}C NMR of **3.23** and **3.23***, there is good alignment of all alkyl and aryl peaks as well as the expected dramatic increase in the carbonyl carbon resonance (Figure 3.2).



CO	Yield
^{12}CO	70%
^{13}CO	60%

Table 3.10 Synthesis of **3.38** and **3.38***

Labeling experiments were also performed with the 7,7'-dimethyl salen **3.4**. Again, we observed carbonylation with both the labeled and unlabeled CO, however a slightly lower yield to form **3.38***. The stacked NMR spectra (Figure 3.3) show good correlation between resonances of **3.38** and **3.38*** and the appearance of the carbonyl carbon peak. These carbonyl resonances at 171 ppm (**3.23***)and 173 ppm (**3.38***) are consistent with the only two other closely related alkoxycarbonyl salen-type cobalt complexes characterized by ^{13}CNMR to our knowledge: Pattenden reported an ethoxycarbonyl salophen complex (160.0 ppm in $CDCl_3$) and Fu reported a methoxycarbonyl salen complex derived from cyclohexanediamine (162.7 ppm in $CDCl_3$).[1–3,23] No major changes in the NMRs are

observed between salen and salophen-based complexes. Consistent with previous reports, the IR, NMR and mass spectrometry data support the assignment of the alkoxycarbonyl complexes as pentacoordinate in weakly coordinating solvents and when isolated as a solid in the absence of additional ligands.

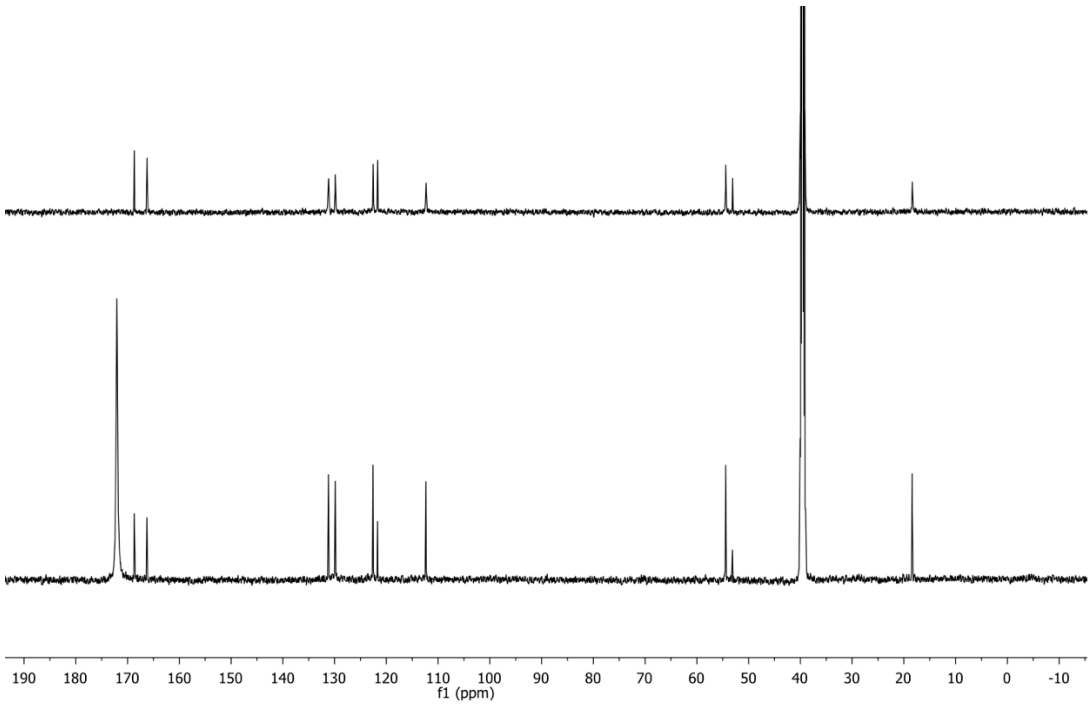
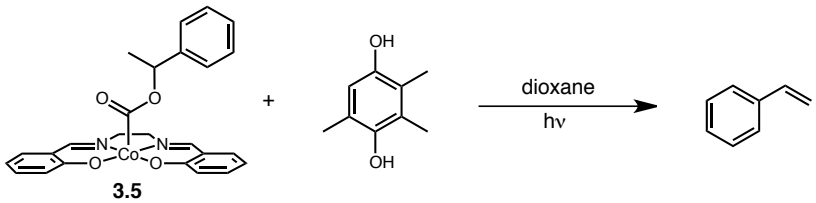


Figure 3.3 ^{13}C NMR of unlabeled **3.38** and labeled **3.38***

3.6 Homolysis and Hydrogen Atom Transfer Reactions

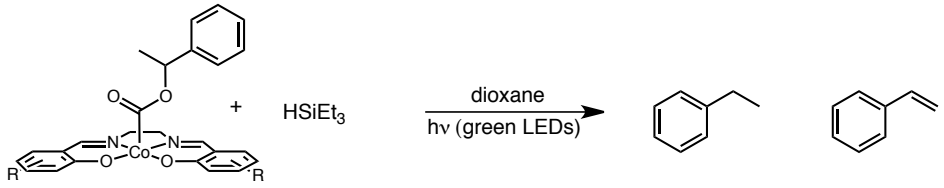
The majority of the homolysis studies and hydrogen atom transfer reactions for salen complexes were performed by Raymond Sullivan. Similar to what was observed with the salophen ligand system (see Chapter 2), studies of homolysis using a standard CFL lamp, in the presence of TEMPO, gave moderate conversion to the TEMPO trapped, decarboxylated, product (58% yield). He also found that thiols promote the conversion of



Light Source	Yield
Green LEDs	17%
450 nm	14%
CFL	14%

Table 3.11 Light source experiments for optimal homolysis. Green LEDs, Kessil 450 nm high intensity LEDs and a standard CFL light bulb were used

complex **3.5** into ethyl benzene and when employing hydroquinones, a selectivity for styrene is observed. Different light sources were examined after optimization of homolysis reaction conditions using trimethylhydroquinone, which favors the production of styrene (Table 3.11). There was a slightly increased conversion using the green LEDs but overall all light sources were very similar. Next, irradiation using the green LEDs was executed in the presence of triethylsilane as a hydrogen atom donor (Table 3.12). With all three salen derivatives tested, there was no significant increase of ethyl benzene product or substantial change in styrene product. In these initial irradiation experiments, no advantage was observed when adding electron-donating groups onto the salen ligand.

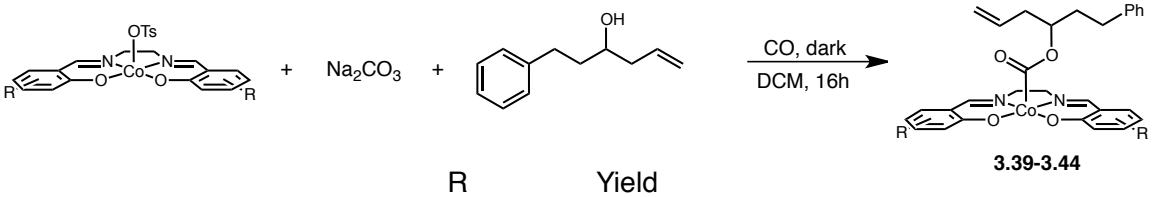


R	Ethylbenzene	Styrene
H	2%	17%
3-OMe	1%	9%
5-Me	3%	7%

Table 3.12 Homolysis of 1-phenethylalkoxycarbonyl cobalt salen complexes

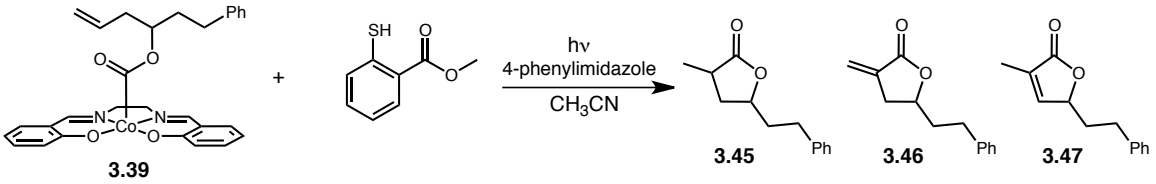
3.7 Lactonization Reactions

As mentioned in Chapter 2, one goal is to perform lactonization under mild conditions and be able to tune the catalyst's selectively to form either the reduced or eliminated product. First alkoxycarbonyl complexes **3.39-3.44** were synthesized by standard carbonylation conditions (5 equiv alcohol, 3 equiv base, 2 atm CO). As expected, the unsubstituted salen and salen ligands with electron-donating groups carbonylated without issue (Table 3.13). Under these conditions, we were also able to carbonylate the more challenging ligands containing bromo and nitro substituents, albeit at low yields. Once complexes **3.39-3.44** were obtained, optimization screens were performed for the homolysis and lactonization. Light sources were examined (Table 3.14) comparing green LEDs, high intensity Kessil lamp emitting at 450 nm and a standard CFL light bulb, and the green LEDs gave a significantly higher yield (41% vs 25%) than the other light sources. Interestingly, even in the presence of a H-donor that was observed to be efficient in earlier



R	Yield
–	**3.39**, 85%
5-Cl	**3.40**, 44%
5-Me	**3.41**, 37%
7-Me	**3.42**, 35%
5-Br	**3.43**, 12%
5-NO_2	**3.44**, 10%

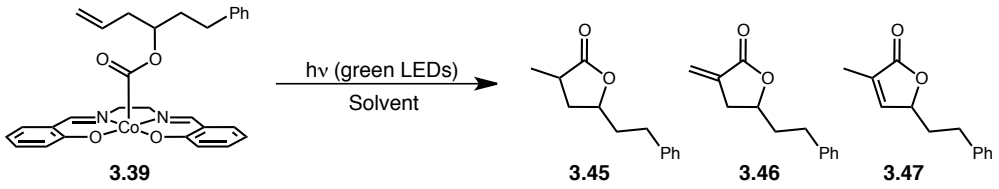
Table 3.13 Redox-neutral carbonylation to alkoxycarbonyl complexes **3.39-3.44**



Light Source	3.46	3.47
Green LEDs	41%	1%
450 nm	25%	2%
CFL	23%	1%

Table 3.14 Homolysis study: light source screen

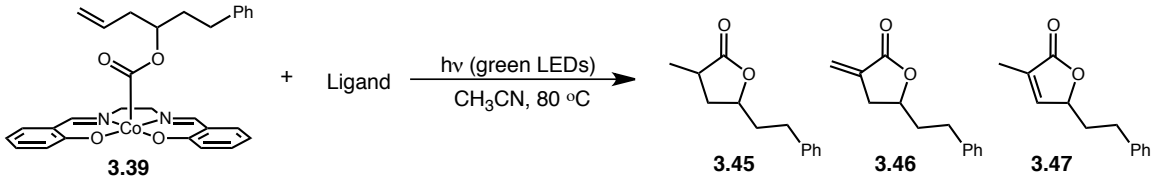
reduction reaction (a thiol), only the β-hydrogen eliminated product **3.46** was observed. A solvent screen in the absence of a H-donor was then performed (Table 3.15). The solvent screen indicated that this reaction generally tolerates changes in solvents, maintaining ~30% yield for toluene, dioxane and DCE. Interestingly, when switching to DCM there is a significant decrease in formation of **3.47** even though in previous reactions DCE and DCM could be used interchangeably. Additionally, in the absence of H-donor and ligand, isomerized product **3.47** was formed almost exclusively compared to β-hydrogen eliminated **3.46** which formed when H-donor and ligand were utilized.



Solvent	3.45	3.46	3.47
Toluene	0%	0%	30%
Dioxane	0%	0%	30%
DCE	0%	7%	26%
CH_3CN	2%	4%	21%
DCM	0%	0%	19%

Table 3.15 Solvent screen for homolysis/lactonization of **3.39**

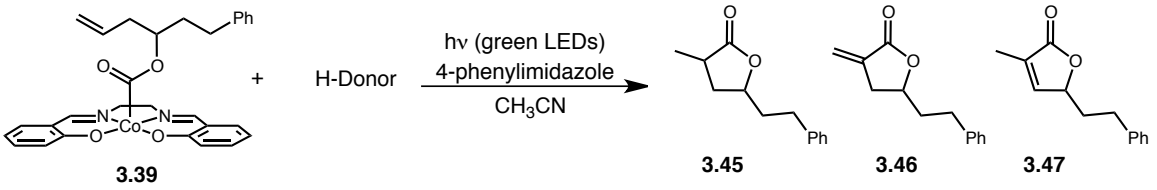
Next, a ligand screen was performed testing the effect of 10 different ligands on the selectivity of products (Table 3.16). All reactions were run in sealed Schlenk tubes under N_2 after three cycles of freeze-pump-thaw to remove any oxygen from the vessel or solvent. Reactions were also run at 80 °C based on work by Dr. Esmat Sodagar. To achieve β-hydrogen eliminated product **3.46**, 4-phenylimidazole was found to be the most efficient with 4-(dimethyl)aminopyridine closely behind. When using imidazole, a modest 24% yield of **3.46** was obtained with a small amount of isomerized product **3.47**. Conversely, high selectivity for isomerized product **3.47** could be accomplished using 1-methylimidazole which gave only small quantities of **3.45** and **3.46**. All other ligands appear to give a mixture of two or three of the products with no significant selectivity for any.



Ligand	**3.45**	**3.46**	**3.47**
4-phenylimidazole	0%	35%	0%
4-(NMe_2)Py	0%	33%	0%
Imidazole	0%	24%	4%
PCy_3	11%	14%	1%
4-phenylpyridine	15%	13%	26%
3-bromopyridine	13%	10%	16%
Pyridine	0%	10%	25%
–	16%	7%	20%
PPh_3	17%	6%	18%
4-*t*-butylpyridine	14%	4%	28%
1-Me-imidazole	3%	3%	30%
KCN	0%	0%	0%

Table 3.16 Ligand screen for homolysis/lactonization of **3.39**

An examination of possible H-donors was also completed using 4-phenylimidazole as the axial ligand (Table 3.17). Under the same reaction conditions previously described,



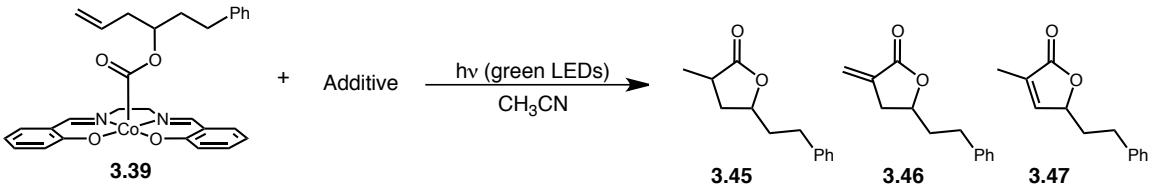
3.39 3.45 3.46 3.47

H-Donor	3.45	3.46	3.47
$HSiEt_3$	0%	0%	30%
$HSi(iPr)_3$	0%	0%	30%
$HSiPh_3$	0%	0%	27%
Trolox	0%	0%	24%
Trimethoxyphenol	0%	39%	0%
–	0%	29%	0%
Trimethylhydroquinone	0%	32%	0%
Ditertbutyl catechol	31%	0%	0%
Sulfinic acid	0%	0%	0%

Table 3.17 H-donor screen for the homolysis/lactonization of **3.39**

silanes and Trolox favor formation of isomerized product **3.47**. Reagents such as trimethylhydroquinone and trimethoxyphenol have little effect on this reaction as they give similar results to the absence of H-donor, namely product **3.46**. Di-*tert*-butyl catechol is the only reagent that appears successful at HAT, giving a 31% yield of reduced product **3.45**. The ability to selectively form each desired product based on ligand and H-donor combinations provides encouragement for the feasibility of this reaction. Regrettably, even with this high selectivity these reactions still remain low-yielding under our stoichiometric reaction conditions.

Next, to probe how this reaction tolerates reagents that will need to be added to render this reaction catalytic, additives such as excess alcohol, Co(II) salen and Co(III)

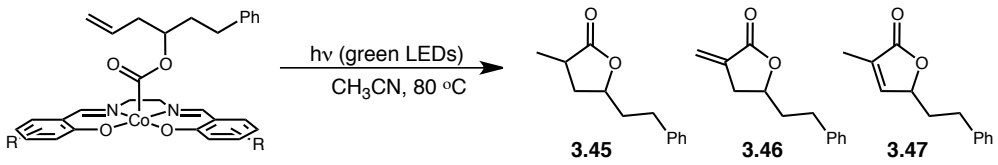


Additive	**3.45**	**3.46**	**3.47**
–	4%	3%	15%
alcohol	3%	4%	15%
Co(II)Salen	2%	2%	19%
CoSalen-OTs	0%	9%	0%

Table 3.18 Additive screen for lactonization reaction

salen-OTs were added the reaction mixture (Table 3.18). There does not appear to be a major effect on the viability of the reaction when alcohol and **3.2** are added to the reaction mixture. This is promising for the feasibility of catalytic studies going forward, however, the reaction with **3.2•OTs** saw a drastic decrease in product formation.

Similar homolysis/lactonization studies were performed with our derivatized salen complexes (Table 3.19). Interestingly, the 5-NO_2 complex **3.44** gave the highest conversion and selectivity of the compounds tested (22% yield, **3.46**). Moreover, the other derivatives tested (**3.41—3.43**) favored the formation of eliminated product **3.46**, with lower overall



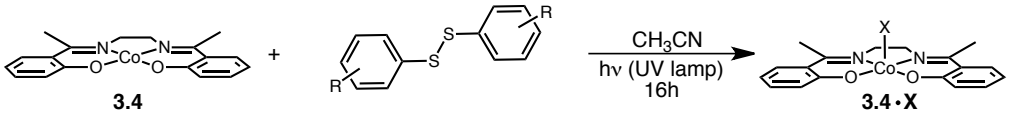
Complex	R	**3.45**	**3.46**	**3.47**
3.44	5-NO_2	0%	22%	0%
3.42	7-Me	3%	16%	8%
3.41	5-Me	0%	10%	0%
3.43	5-Br	3%	10%	3%
3.40	5-Cl	1%	5%	7%

Table 3.19 Homolysis/lactonization study of salen derivatives

conversion. Derivative **3.40** showed a general lack of selectivity between eliminated product **3.46** and isomerized lactone **3.47**. Ultimately, none of the salen derivatives demonstrated different innate selectivity between possible lactone products than the unsubstituted complex.

3.8 Turnover Experiments and One Pot Reactions

After establishing methods for the carbonylation and homolysis of these cobalt salen complexes, we examined the potential to convert the stoichiometric reactions studied into a catalytic process. One important component of that study is the re-oxidation of our cobalt(II) salen produced after homolysis. Based on our proposed catalytic cycle, we envisioned that the thiyl radical resulting from HAT would get reduced by Co(II) to produce a thiolate anion and Co(III) species, turning over the catalytic cycle. To study this hypothesis, we generated thiyl radicals by irradiating disulfides with UV light[24,25] in the presence of Co(II)salen derivatives (Table 3.20). Oxidation was determined by ^{1}H NMR vs benzodioxole as an internal standard. Oxidation can be determined by the appearance of NMR resonances, as **3.4** is paramagnetic and oxidized **3.4•X** is diamagnetic. Unfortunately, the axial ligand of oxidized product **3.4•X** could not be determined. It was clear by ^{1}H

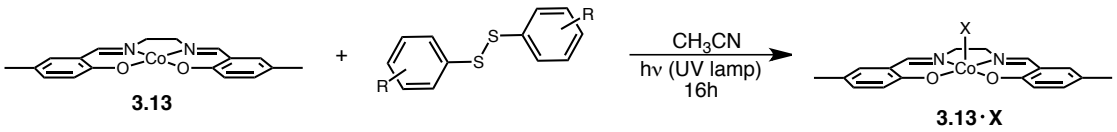


3.4 + Disulfide → **3.4•X**

Disulfide	**3.4•X**
2-Chloro	25%
4-Nitro	25%
2,6-Dichloro	20%

Table 3.20 Oxidation of **3.4** by thiyl radical. Yields calculated against internal standard in ^{1}H NMR

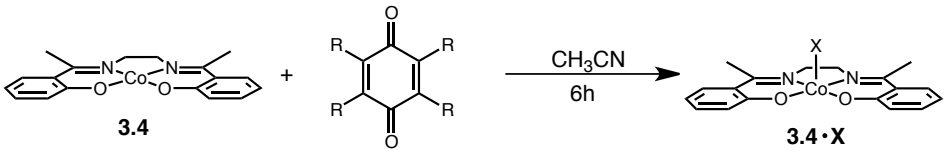
NMR that the product was not the sulfide complex (X = SAr) by comparison to an authentic standard, however the nature of X was not elucidated. Oxidation under these conditions are not highly efficient, resulting in a modest 25% yield.



Disulfide	**3.13•X**
4-Nitro	37%
4-Chloro	29%
2,6-Dichloro	21%
unsubstituted	11%
2-Chloro	7%

Table 3.21 Oxidation of **3.13** by substituted disulfides

Oxidation reactions were repeated with complex **3.13** and a larger range of substituted disulfides (Table 3.21). Unsurprisingly, the more electron-withdrawing disulfides give higher conversion to **3.13•X** as they are more oxidizing.[26] The best



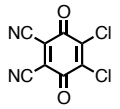
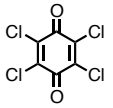
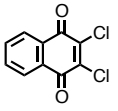
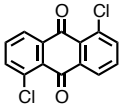
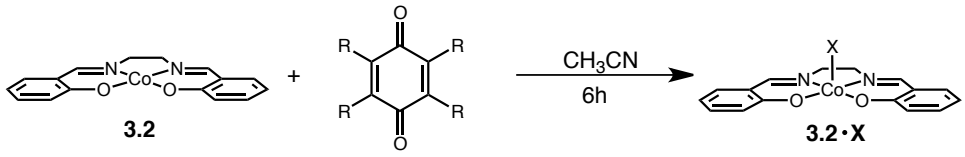
Quinone	E^1_{red}[a]	**3.4•X**
	0.5	100%
	0.03	59%
	−0.52	57%
	−0.7	0%

Table 3.22 Oxidation of **3.4** with quinones. a) Values given in V vs. SCE[28]

oxidation under these conditions was achieved with 4-nitrophenyldisulfide (37% yield) but was still inefficient even on our easiest to oxidize complexes. To overcome the slow reaction times and low conversion to oxidized products, we shifted focus to more oxidizing conditions.

Quinones were of interest to study as they have favorable oxidation potentials and are highly tunable.[27] Initial studies oxidizing complex **3.4** showed promising results, with full conversion to **3.4•X** within 6 hours (Table 3.22). Due to the ease of oxidation of complex **3.4** it is surprising that chloranil did not form oxidized complex **3.4•X** at a higher conversion. It is likely that some decomposition occurred due to the instability of complex **3.4** under these reaction conditions. Further studies of the oxidation of salen complexes was performed with complexes **3.2** (Table 3.23) and **3.14** (Table 3.24).



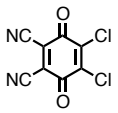
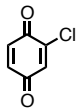
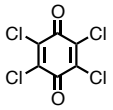
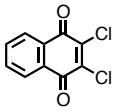
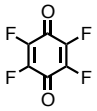
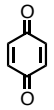
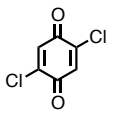
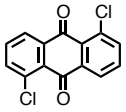
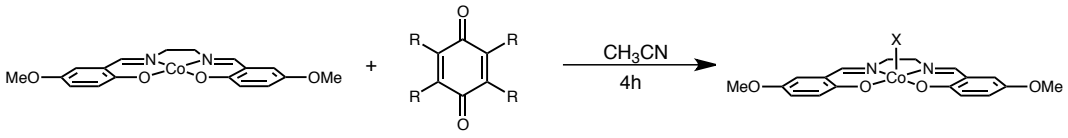
Quinone	E^1_{red}[a]	3.2•X	Quinone	E^1_{red}[a]	3.2•X
	0.5	100%		−0.35	68%
	0.03	100%		−0.52	25%
	0.003	100%		−0.5	0%
	−0.18	100%		−0.7	0%

Table 3.23 Oxidation of **3.2** with quinones. a) Values given in V vs. SCE[28]



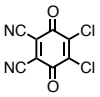
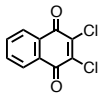
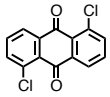
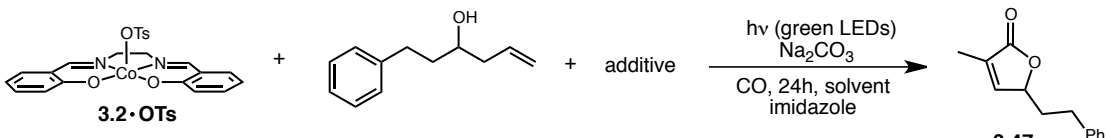
Quinone	E^1_{red}[a]	**3.14•X**	Quinone	E^1_{red}[a]	**3.2•X**
	0.5	100%		−0.35	58%
	0.03	100%		−0.52	0%
	0.003	100%		−0.5	0%
	−0.18	100%		−0.7	0%

Table 3.24 Oxidation of **3.14** with quinones. a) Values given in V vs. SCE[28]

Efficient oxidation was achieved for both complexes with 2,5-dichloro-, tetrafluoro-, tetrachloro-, and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). Oxidation with 2-chloro-1,4-benzoquinone was less effective but still proceeded with good conversion (58-68% yield). Oxidation with 2,3-dichloro-1,4-naphthoquinone was only mildly effective to form oxidized complex **3.2•X** and ineffective at oxidizing complex **3.14**. Predictably, less oxidizing unsubstituted 1,4-benzoquinone (-0.5V vs SCE) produced no oxidized product.[27]

Finally, we tested the carbonylation/lactonization reaction of **3.2•OTs** in the presence of tetrachlorohydroquinone and tetrachlorobenzoquinone. Since quinones were highly efficient at oxidation and hydroquinones had high selectivity and conversion to lactone **3.46** the addition of them into a one pot reaction was promising. However, attempts



Additive	Solvent	3.47
Tetrachlorohydroquinone	CH_3CN	0%
Tetrachlorohydroquinone	DCM	2%
Tetrachlorobenzoquinone	CH_3CN	0%
Tetrachlorobenzoquinone	DCM	0%

Table 3.25 One-pot carbonylation/lactonization reaction with quinones and hydroquinones

at a one pot carbonylation/lactonization all met with failure. Not only was there no turnover observed, but there was a complete inhibition of the reaction.

3.9 Conclusions

A carbonylation method has been developed from both Co(III) and Co(II) precursors, requiring only 1 atm of CO and a weak base or oxidant, respectively, and avoiding strong reducing agents and sensitive Co(I) intermediates. Under these mild conditions a general scope of alcohols can be integrated into these complexes. Electron-rich and electron-poor cobalt salen complexes were synthesized and carbonylated. Full characterization and labeling experiments have confirmed incorporation of the carbon monoxide moiety. Additionally, homolysis studies with suitable complexes demonstrated the potential of this method for the formation of lactones, with high selectivity between possible products though at low conversion. Oxidation of Co(II)salen complexes using disulfides and quinones demonstrate plausible turnover when applied to the catalytic system. Unfortunately, one pot reactions are currently unattainable through this ligand system either through external oxidants or starting from our Co(III) precursors.

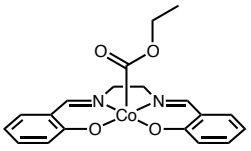
3.10 Experimental

All reactions were carried out in oven dried or flame dried glassware charged with a magnetic stir bar, were prepared under inert nitrogen atmosphere, and subsequently degassed with carbon monoxide. Solvents were dried by passage through columns of activated alumina. Anhydrous dichloroethane (DCE) was dried over 5 Å sieves to remove trace amounts of methanol. Commercially available alcohols were distilled from calcium hydride prior to use. Protected alcohols were synthesized by known literature procedures. Co(II)salen, Co(II)salph, Co(III)salen-OTs, Co(III)salen-I, Co(III)salen-Br(PPh_3) were prepared according to known literature procedures.

Procedure A: Redox-neutral carbonylation: To a mixture of Co(III)salen-OTs (**3.4•OTs**) and Na_2CO_3 was added 8 mL CH_2Cl_2 and the reaction mixture was purged with CO (balloon) for 10 s. The reaction mixture was then treated with the respective alcohol and stirred for the indicated time in the dark, at room temperature, under 1.0 atm CO. Reactions were tracked by TLC (3% MeOH in CH_2Cl_2). Upon completion, the product was precipitated by addition of heptane and the suspension was filtered through Celite, washing several times with heptane to remove excess unreacted alcohol. Subsequent washing with CH_2Cl_2 separated the product from remaining Co(III) starting material. The green filtrate was washed three times with dilute sodium bicarbonate, dried with sodium sulfate and concentrated to yield an orange solid. No further purification was required.

Procedure B: Oxidative carbonylation of salen: To a mixture of Co(II)salen (**3.2**) and potassium persulfate was added CH_2Cl_2 and the reaction mixture was purged with CO (balloon) for 10 s. The reaction mixture was then treated with the respective alcohol and

stirred for the indicated time in the dark, at room temperature, under 1 atm CO. Reactions were tracked by TLC (3% MeOH in CH_2Cl_2). Upon completion, the product was precipitated by addition of heptane and filtered through Celite, washing several times with heptane to remove excess unreacted alcohol. Subsequent washing with CH_2Cl_2 separated the product from remaining Co(II) starting material. The green Co(III) filtrate was concentrated to yield an orange solid. No further purification was required.

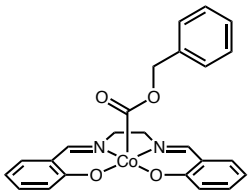


Ethoxycarbonyl-cobalt salen (3.21)

Prepared with alcohol as solvent: 51 mg **3.2•OTs** (0.10 mmol, 1.0 equiv) was dissolved in ethanol (4.5 mL) and degassed with carbon monoxide for 10 s. The reaction mixture was treated with 1.0 mL of sodium ethoxide solution (1.0 M in ethanol, 1.0 mmol, 10. equiv) and was stirred in the dark, under 1 atm CO at room temperature for 24 hours. The product was precipitated out upon addition of water and sonication. Filtration afforded an orange crystalline solid (41 mg, 0.1 mmol, 99%).

Prepared via general redox neutral procedure A using 99 mg **3.2•OTs** (0.20 mmol, 1.0 equiv), 64 mg Na_2CO_3 (0.60 mmol, 3.0 equiv) and 58 μL ethanol (1.0 mmol, 5.0 equiv). The reaction was stirred for 24 hours and afforded an orange crystalline solid (67 mg, 0.17 mmol, 84%). IR (film) 2930–2969, 1631, 1601, 1451, 1059 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.98 (s, 2H), 7.18 (d, J = 7.7 Hz, 2H), 7.11 (t, J = 7.6 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 6.40 (t, J = 6.9 Hz, 2H), 3.96 (q, J = 7.0 Hz, 2H), 3.64 – 3.72 (m, 2H), 3.49 – 3.57 (m, 2H), 0.69 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.1, 163.4,

133.6, 132.6, 121.6, 120.5, 112.5, 61.4, 57.9, 14.4; HRMS (ESI) *m / z* calcd for $C_{19}H_{19}CoN_2O_4Na$ $(M + Na)^+$ 421.0569, found 421.0574.



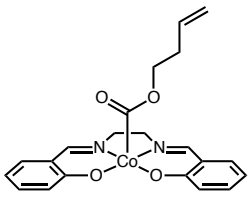
Benzyloxycarbonyl-cobalt salen (3.22)

Prepared with alcohol as solvent: 51 mg **3.2•OTs** (0.10 mmol, 1.0 equiv) in 4.5 mL benzyl alcohol was degassed with carbon monoxide for 10 s. The reaction mixture was then treated with 1.0 mL of sodium benzyloxide solution (1.0 M in benzyl alcohol, 1.0 mmol, 10. equiv) and was stirred in the dark, under 1 atm CO at room temperature for 24 hours. Upon completion, the reaction mixture was added to heptane and DCM was introduced until the two layers became miscible. After sonication, the mixture was filtered to afford an orange crystalline solid (35 mg, 0.08 mmol, 76%).

Prepared via redox neutral general procedure A using 51 mg **3.2•OTs** (0.10 mmol, 1.0 equiv), 32 mg Na_2CO_3 (0.30 mmol, 3.0 equiv) and 52 μL benzyl alcohol (0.50 mmol, 5.0 equiv). The reaction was stirred for 24 hours and afforded an orange crystalline solid (44 mg, 0.096 mmol, 96%).

Prepared via general salen oxidative procedure B using 51 mg **3.2** (0.15 mmol, 1.0 equiv), 120 mg $K_2S_2O_8$ (0.46 mmol, 3.0 equiv), and 55 μL benzyl alcohol (0.46 mmol, 3.0 equiv) in 7.5 mL CH_2Cl_2. Reaction was stirred for 2 days and afforded an orange crystalline solid (68 mg, 0.147 mmol, 98%). IR (film) 2933–3054, 1681, 1599, 1453, 1018 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.99 (s, 2H), 7.04 – 7.24 (m, 7H), 6.84 (s, 4H), 6.43 (t, J = 6.7 Hz, 2H), 5.03 (s, 2H), 3.68 (d, J = 6.6 Hz, 2H), 3.51 (d, J = 6.6 Hz, 2H); ^{13}C NMR (125

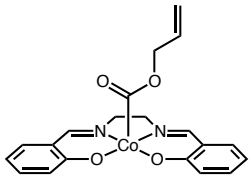
MHz, DMSO-d_6) δ 166.5, 164.1, 138.1, 134.1, 133.2, 128.4, 127.3, 126.8, 122.2, 120.8, 113.1, 67.1, 58.4; HRMS (ESI) *m / z* calcd for $C_{24}H_{21}CoN_2O_4$ $(M + Na)^+$ 483.0726, found 483.0728.



3-Buten-1-yloxycarbonyl-cobalt salen (3.23)

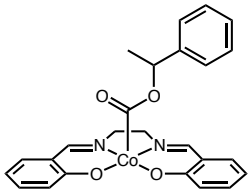
Prepared via redox neutral general procedure A using 99 mg **3.2•OTs** (0.20 mmol, 1.0 equiv), 64 mg Na_2CO_3 (0.60 mmol, 3.0 equiv) and 86 μL 3-buten-1-ol (1.0 mmol, 5.0 equiv). The reaction was stirred for 6 hours and afforded an orange crystalline solid (65 mg, 0.15 mmol, 76%).

Prepared under general salen oxidative procedure B using 100 mg **3.2** (0.30 mmol, 1.0 equiv), 250 mg $K_2S_2O_8$ (0.90 mmol, 3.0 equiv), and 77 μL 3-buten-1-ol (0.90 mmol, 3.0 equiv) in 15 mL CH_2Cl_2. Reaction was stirred for 24 hours and afforded an orange crystalline solid (130 mg, 0.19 mmol, 62%). IR (film) 2851–3042, 1677, 1601, 1444, 1059 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.97 (s, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.11 (t, *J* = 7.5 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 6.41 (t, *J* = 7.2 Hz, 2H), 5.39 (m, 1H), 4.75 – 4.84 (m, 2H), 3.97 (t, *J* = 6.3 Hz, 2H), 3.68 (d, *J* = 6.7 Hz, 2H), 3.52 (d, *J* = 6.3 Hz, 2H), 1.85 (q, *J* = 6.4 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.1, 163.5, 134.9, 133.5, 132.6, 121.6, 120.5, 116.2, 112.5, 64.9, 58.0, 33.2; HRMS (ESI) *m / z* calcd for $C_{21}H_{21}CoN_2O_4Na$ $(M + Na)^+$ 447.0726, found 447.0736.



Allyloxycarbonyl-cobalt salen (3.24)

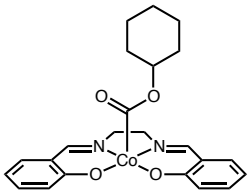
Prepared via redox neutral general procedure A using 99 mg **3.2•OTs** (0.20 mmol, 1.0 equiv), 64 mg Na_2CO_3 (0.60 mmol, 3.0 equiv) and 68 μL allyl alcohol (1.0 mmol, 5.0 equiv). The reaction was stirred for 6 hours and afforded an orange crystalline solid (53 mg, 0.13 mmol, 64%). IR (film) 2851–2921, 1674, 1626, 1598, 1448, 1058 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.00 (s, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.12 (t, *J* = 6.8 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 6.41 (t, *J* = 7.2 Hz, 2H), 5.49 (m, 1H), 4.83 (dd, *J* = 10.6, *J* = 1.5 Hz, 1H), 4.79 (dd, *J* = 17.4, *J* = 1.8 Hz, 1H), 4.48 (d, *J* = 4.7 Hz, 2H), 3.69 (d, *J* = 6.8 Hz, 2H), 3.54 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.1, 163.5, 133.7, 133.6, 132.7, 121.7, 120.4, 115.1, 112.5, 65.5, 58.0; HRMS (ESI) *m / z* calcd for $C_{21}H_{21}CoN_2O_4Na$ $(M + Na)^+$ 433.0569, found 433.0556.



1-Phenylethyloxycarbonyl-cobalt salen (3.25)

Prepared under general salen oxidative conditions B using 100 mg **3.2** (0.30 mmol, 1.0 equiv), 250 mg $K_2S_2O_8$ (0.90 mmol, 3.0 equiv), and 110 μL 1-phenylethanol (0.90 mmol, 3.0 equiv). Reaction was stirred for 2 days and afforded an orange crystalline solid (130 mg, 0.27 mmol, 90%).

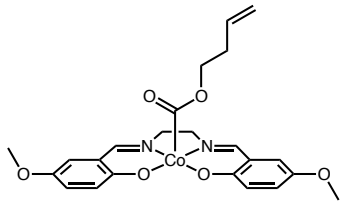
Prepared via general redox neutral conditions A from **3.2•OTs** using 99 mg (0.20 mmol, 1.0 equiv), 64 mg Na_2CO_3 (0.60 mmol, 3.0 equiv) and 120 μL 1-phenylethanol (1.0 mmol, 5.0 equiv) in 7.5 mL CH_2Cl_2. The reaction was stirred for 6.5 hours and afforded an orange crystalline solid (64 mg, 0.14 mmol, 68%). IR (film) 2928–3041, 1674, 1602, 1451, 1038 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.01 (s, 2H), 7.21 (d, *J* = 7.5 Hz, 2H), 7.06 – 7.18 (m, 5H), 6.81–6.87 (m, 4H), 6.43 (d, *J* = 6.8 Hz, 2H), 5.83 (d, *J* = 6.9 Hz, 1H), 3.68 (d, *J* = 5.1 Hz, 2H), 3.44 (d, *J* = 6.7 Hz, 2H), 0.96 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.1, 163.5, 143.3, 133.5, 127.9, 125.3, 121.7, 120.6, 112.5, 72.6, 57.9, 23.1; HRMS (ESI) *m / z* calcd for $C_{25}H_{23}CoN_2O_4$ $(M + Na)^+$ 497.0882, found 497.0892.



Cyclohexyloxycarbonyl-cobalt salen (3.26)

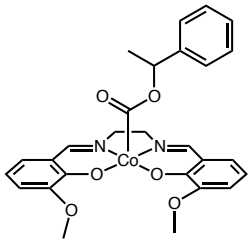
Prepared via redox neutral general procedure A using 99 mg **3.2•OTs** (0.20 mmol, 1.0 equiv), 64 mg Na_2CO_3 (0.60 mmol, 3.0 equiv) and 110 μL cyclohexanol (1.0 mmol, 5.0 equiv). The reaction was stirred for 6 hours and afforded an orange crystalline solid (77 mg, 0.17 mmol, 85%). IR (film) 2857–2931, 1677, 1630, 1599, 1452, 1054 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6 δ 7.99 (s, 6H), 7.18 (dd, *J* = 7.7, 1.5 Hz, 6H), 7.11 (dd, *J* = 11.1, *J* = 4.2 Hz, 6H), 6.82 (d, *J* = 8.5 Hz, 6H), 6.40 (t, *J* = 7.2 Hz, 6H), 4.84 (s, 3H), 3.70 (dd, *J* = 12.8, 6.5 Hz, 6H), 3.50 (dd, *J* = 12.8, 6.6 Hz, 6H), 1.27 (s, 7H), 1.17 – 1.01 (m, 24H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.1, 163.4, 133.5, 132.6, 121.6, 120.6, 112.4, 72.3, 58.0,

30.9, 25.1, 21.6; HRMS (ESI) *m / z* calcd for $C_{21}H_{21}CoN_2O_4Na$ $(M + Na)^+$ 475.1039, found 475.1038.



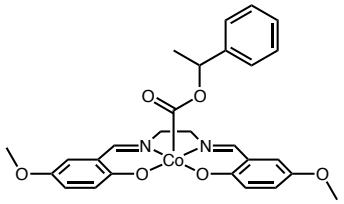
3-Buten-1-yloxycarbonyl-cobalt 5-methoxy-salen (3.27)

Prepared via redox neutral general procedure A using 140 mg **3.14•OTs** (0.25 mmol, 1.0 equiv), 79 mg Na_2CO_3 (0.75 mmol, 3.0 equiv) and 110 μL 3-buten-1-ol (1.25 mmol, 5 equiv). The reaction was stirred for 6 hours and afforded an orange crystalline solid (81 mg, 0.18 mmol, 70%).^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (s, 2H), 6.85 (dd, J = 9.1, 3.2 Hz, 2H), 6.80 – 6.72 (m, 4H), 5.41–5.32 (m, 1H) 4.87 – 4.76 (m, 2H), 3.98 (t, J = 6.4 Hz, 2H), 3.66 (s, 6H), 1.92 – 1.84 (m, 2H).



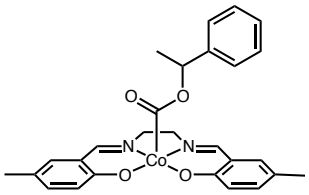
1-Phenylethyloxycarbonyl-cobalt 3-methoxy-salen (3.30)

Prepared via general redox neutral conditions A from **3.18•OTs** using 140 mg (0.25 mmol, 1.0 equiv), 81 mg Na_2CO_3 (0.75 mmol, 3.0 equiv) and 150 μL 1-phenylethanol (1.25 mmol, 5.0 equiv) in 10 mL CH_2Cl_2. The reaction was stirred for 2 days and afforded an orange crystalline solid (95 mg, 0.18 mmol, 71%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 – 8.07 (m, 2H), 7.53 – 7.45 (m, 2H), 7.17 – 7.08 (m, 4H), 6.94 – 6.82 (m, 6H), 6.49 (td, J = 7.8, 1.8 Hz, 2H), 5.83 (q, J = 6.5 Hz, 1H), 1.01 (d, J = 6.5 Hz, 2H).



1-Phenylethyloxycarbonyl-cobalt 5-methoxy-salen (3.31)

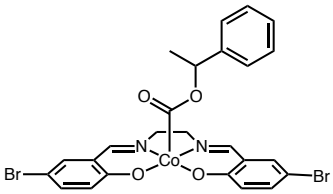
Prepared via general redox neutral conditions A from **3.14•OTs** using 140 mg (0.25 mmol, 1.0 equiv), 81 mg Na_2CO_3 (0.75 mmol, 3.0 equiv) and 150 μL 1-phenylethanol (1.25 mmol, 5.0 equiv) in 10 mL CH_2Cl_2. The reaction was stirred for 2 days and afforded an orange crystalline solid (80 mg, 0.15 mmol, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 2H), 7.16 – 7.03 (m, 5H), 6.92 (ddd, *J* = 12.7, 9.1, 3.1 Hz, 2H), 6.86 – 6.78 (m, 2H), 6.40 (dd, *J* = 9.9, 3.1 Hz, 2H), 5.95 (q, *J* = 6.5 Hz, 1H), 4.12 – 3.84 (m, 2H), 3.70 (d, *J* = 11.7 Hz, 6H), 3.58 (m, 2H), 1.08 (d, *J* = 6.5 Hz, 3H).



1-Phenylethyloxycarbonyl-cobalt 5-methyl-salen (3.32)

To a mixture of Co(III)salen-OTs (**3.13•OTs**) 130 mg (0.25 mmol, 1.0 equiv) and 81 mg Na_2CO_3 (0.75 mmol, 3.0 equiv) was added 10 mL CH_2Cl_2 and the reaction mixture was degassed with three cycles of freeze-pump-thaw and pressurized with 2 atm of CO. The reaction mixture was then treated with 150 μL 1-phenylethanol (1.25 mmol, 5.0 equiv and stirred for the 2 days in the dark, at room temperature, under 2 atm CO. Upon completion, the product was precipitated by addition of heptane and the suspension was filtered through Celite, washing several times with heptane to remove excess unreacted

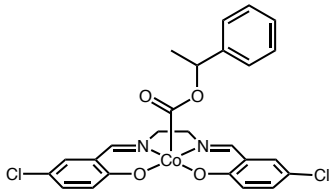
alcohol. Subsequent washing with CH_2Cl_2 separated the product from remaining Co(III) starting material. The green filtrate was washed three times with dilute sodium bicarbonate, dried with sodium sulfate and concentrated to yield an orange crystalline solid (65 mg, 0.13 mmol, 52%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 6.2 Hz, 2H), 7.41 – 7.27 (m, 2H), 7.19 – 7.07 (m, 5H), 6.93 (d, *J* = 8.1 Hz, 2H), 6.88 – 6.82 (m, 2H), 6.00 (q, *J* = 6.5 Hz, 1H), 3.85 (m, 2H), 3.64 (m, 1H), 3.53 (m, 1H), 2.24 (s, 6H), 1.15 (d, *J* = 6.5 Hz, 3H).



1-Phenylethyloxycarbonyl-cobalt 5-bromo-salen (3.33)

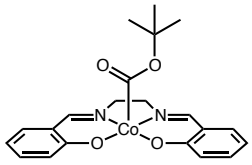
To a mixture of Co(III)salen-OTs (**3.19•OTs**) 130 mg (0.25 mmol, 1.0 equiv) and 81 mg Na_2CO_3 (0.75 mmol, 3.0 equiv) was added 10 mL CH_2Cl_2 and the reaction mixture was degassed with three cycles of freeze-pump-thaw and pressurized with 2 atm of CO. The reaction mixture was then treated with 150 μL 1-phenylethanol (1.25 mmol, 5.0 equiv and stirred for the 2 days in the dark, at room temperature, under 2 atm CO. Upon completion, the product was precipitated by addition of heptane and the suspension was filtered through Celite, washing several times with heptane to remove excess unreacted alcohol. Subsequent washing with CH_2Cl_2 separated the product from remaining Co(III) starting material. The green filtrate was washed three times with dilute sodium bicarbonate, dried with sodium sulfate and concentrated to yield an orange crystalline solid (31 mg, 0.05 mmol, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 2H), 7.00 (dt, *J* = 11.9, 7.3 Hz, 4H),

6.90 – 6.79 (m, 3H), 6.70 (d, J = 7.5 Hz, 2H), 6.21 – 6.09 (m, 2H), 5.82 (q, J = 6.5 Hz, 1H), 3.57 (s, 2H), 3.49 (s, 2H), 0.96 (d, J = 6.5 Hz, 3H).



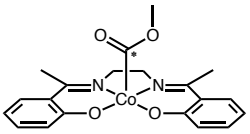
1-Phenylethyloxycarbonyl-cobalt 5-chloro-salen (3.34)

To a mixture of Co(III)salen-OTs (**3.16•OTs**) 140 mg (0.25 mmol, 1.0 equiv) and 81 mg Na_2CO_3 (0.75 mmol, 3.0 equiv) was added 10 mL CH_2Cl_2 and the reaction mixture was degassed with three cycles of freeze-pump-thaw and pressurized with 2 atm of CO. The reaction mixture was then treated with 150 μL 1-phenylethanol (1.25 mmol, 5.0 equiv and stirred for the 2 days in the dark, at room temperature, under 2 atm CO. Upon completion, the product was precipitated by addition of heptane and the suspension was filtered through Celite, washing several times with heptane to remove excess unreacted alcohol. Subsequent washing with CH_2Cl_2 separated the product from remaining Co(III) starting material. The green filtrate was washed three times with dilute sodium bicarbonate, dried with sodium sulfate and concentrated to yield an orange crystalline solid (100 mg, 0.18 mmol, 74%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (s, 2H), 7.30 (d, J = 2.8 Hz, 2H), 7.14 (m, 5H), 6.92 – 6.77 (m, 4H), 5.86 (q, J = 6.6 Hz, 1H), 3.75 – 3.64 (m, 2H), 3.46 – 3.36 (m, 2H), 1.02 (d, J = 6.6 Hz, 3H).



tert-Butyloxycarbonyl-cobalt salen (3.36)

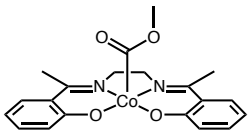
Prepared according to general salen oxidative procedure B using 100 mg **3.2** (0.30 mmol, 1.0 equiv), 250 mg $K_2S_2O_8$ (0.90 mmol, 3.0 equiv), and 86 μL *tert*-butyl alcohol (0.90 mmol, 3.0 equiv) in 15 mL CH_2Cl_2. Reaction was stirred for 2 days and afforded an orange crystalline solid (110 mg, 0.26 mmol, 86%). IR (film) 2926-3051, 1672, 1606, 1437, 1070 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.97 (s, 2H), 7.17 (d, J = 7.0 Hz, 2H), 7.10 (t, J = 7.1 Hz, 2H), 6.83 (d, J = 8.2 Hz, 2H), 6.39 (t, J = 7.3 Hz, 2H), 3.69 (d, J = 6.3 Hz, 2H), 3.50 (d, J = 6.3 Hz, 2H), 0.97 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.1, 163.2, 133.4, 132.4, 121.6, 120.8, 112.3, 80.5, 58.0, 27.7; HRMS (ESI) *m / z* calcd for $C_{21}H_{23}CoN_2O_4$ $(M + Na)^+$ 449.0882, found 449.0893.



^{13}C-Methoxycarbonyl-cobalt 7,7'-dimethylsalen (3.38*)

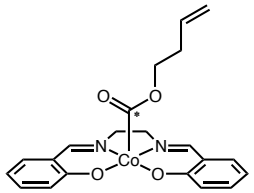
To a mixture of 91 mg 7,7'-dimethylsalen-cobalt **3.4** (0.25 mmol, 1.0 equiv) and 130 mg potassium persulfate (0.5 mmol, 2.0 equiv) was added 13 mL CH_2Cl_2 (degassed) and the reaction mixture was bubbled with ^{13}CO. The reaction mixture was then treated with methanol (51 μL, 1.25 mmol) and stirred overnight at room temperature, under 1 atm CO, in the dark. Reaction afforded a red crystalline solid (61 mg, 0.15 mmol, 60%). IR (film) 2854-3057, 1596, 1532, 1441, 1043 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.49 (d,

J = 8.0 Hz, 2H), 7.04 (t, *J* = 7.5 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.39 (t, *J* = 7.3 Hz, 2H), 3.77 (d, *J* = 7.2 Hz, 2H), 3.60 (d, *J* = 7.4 Hz, 2H), 3.39 (d, *J* = 3.9 Hz, 3H), 2.47 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.1 (C=O), 168.7, 166.3, 131.2, 129.8, 122.6, 121.7, 112.4, 54.4, 53.1, 18.4; HRMS (ESI) *m / z* calcd for $C_{19}{}^{13}C\ H_{21}CoN_2O_4Na$ (M + Na)$^+$436.0760, found 436.0775.



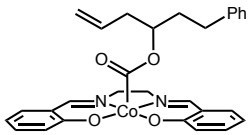
Methoxycarbonyl-cobalt 7,7'-dimethylsalen (3.38)

To a mixture of 91 mg 7,7'-dimethylsalen-cobalt **3.4** (0.25 mmol, 1.0 equiv) and 130 mg potassium persulfate (0.5 mmol, 2.0 equiv) was added 13 mL CH_2Cl_2 (degassed) and the reaction mixture was bubbled with CO. The reaction mixture was then treated with methanol (51 μL, 1.25 mmol) and stirred overnight at room temperature, under 1 atm CO, in the dark. Reaction afforded a red crystalline solid (72 mg, 0.18 mmol, 70%). IR (film) 2939–3054, 1675, 1656, 1441, 1036 ; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.04 (t, *J* = 7.5 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.39 (t, *J* = 7.5 Hz, 2H), 3.73 – 3.80 (m, 2H), 3.57 – 3.64 (m, 2H), 3.39 (s, 3H), 2.47 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.6, 166.2, 131.2, 129.8, 122.5, 121.7, 112.3, 54.4, 53.1, 18.4; HRMS (ESI) *m / z* calcd for $C_{28}H_{21}CoN_2O_4Na$ (M + Na)$^+$ 435.0726, found 435.0746.



^{13}C-3-Buten-1-yloxycarbonyl-cobalt salen (3.23*)

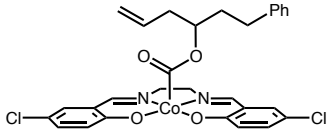
Prepared via redox neutral general procedure A using 99 mg **3.2•OTs** (0.20 mmol, 1.0 equiv), 64 mg Na_2CO_3 (0.60 mmol, 3.0 equiv) and 86 μL 3-buten-1-ol (1.0 mmol, 5.0 equiv). Reaction was purged with ^{13}C carbon monoxide for 10 s and the reaction mixture was stirred for 16 hours and afforded an orange crystalline solid (38 mg, 0.09 mmol, 44%). IR (film) 2848–3037, 1593, 1436, 1048 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.97 (s, 2H), 7.18 (dt, J = 7.9, 1.8 Hz, 2H), 7.18 – 7.07 (m, 2H), 6.82 (d, J = 8.4 Hz, 2H), 6.40 (q, J = 6.3 Hz, 2H), 5.50 – 5.30 (m, 1H), 4.89 – 4.67 (m, 2H), 4.05 – 3.89 (m, 2H), 3.67 (m, 2H), 3.53 (m, 2H), 1.85 (q, J = 6.6 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.6, 163.9, 135.4, 134.0, 133.1, 122.1, 120.9, 116.7, 112.9, 65.4, 58.4, 33.7. HRMS (ESI) *m / z* calcd for $C_{20}(^{13}C)H_{21}CoN_2O_4Na$ $(M + Na)^+$ 448.0779, found 448.0768.



1-phenylhex-5-en-3-oxycarbonyl-cobalt salen (3.39)

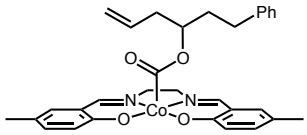
Prepared via redox neutral general procedure A using 25 mg **3.2•OTs** (0.05 mmol, 1.0 equiv), 16 mg Na_2CO_3 (0.15 mmol, 3.0 equiv) and 44 μL 1-phenylhex-5-en-3-ol (0.25 mmol, 5.0 equiv). The reaction was stirred for 24 hours and afforded an orange crystalline solid (24 mg, 0.04 mmol, 85%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (s, 2H), 7.27 – 7.16 (m, 5H), 7.16 – 7.07 (m, 4H), 6.98 – 6.91 (m, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.47 – 6.35

(m, 2H), 5.51 – 5.36 (m, 1H), 4.86 (d, J = 9.0 Hz, 1H), 3.77 – 3.67 (m, 2H), 3.57 (q, J = 6.1 Hz, 2H), 2.32 – 2.12 (m, 2H), 1.96 (m, 2H), 1.46 – 1.19 (m, 2H).



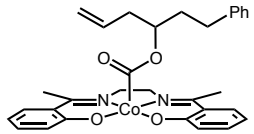
1-phenylhex-5-en-3-oxycarbonyl-cobalt 5-chloro-salen (3.40)

Prepared via redox neutral general procedure A using 140 mg **3.16•OTs** (0.25 mmol, 1.0 equiv), 81 mg Na_2CO_3 (0.75 mmol, 3.0 equiv) and 230 μL 1-phenylhex-5-en-3-ol (1.25 mmol, 5.0 equiv). The reaction was stirred for 24 hours and afforded an orange crystalline solid (66 mg, 0.10 mmol, 44%).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (s, 2H), 7.33 – 7.18 (m, 5H), 7.17 – 7.05 (m, 4H), 6.93 (d, J = 7.5 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 5.42 (m, 1H), 4.95 – 4.86 (m, 2H), 3.72 (m, 2H), 3.55 (m, 2H) 2.30 – 2.12 (m, 2H), 2.02 (m, 2H), 1.44 – 1.24 (m, 2H).



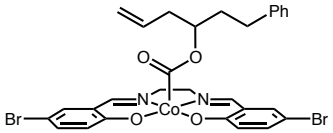
1-phenylhex-5-en-3-oxycarbonyl-cobalt 5-methyl-salen (3.41)

Prepared via redox neutral general procedure A using 130 mg **3.13•OTs** (0.25 mmol, 1.0 equiv), 81 mg Na_2CO_3 (0.75 mmol, 3.0 equiv) and 230 μL 1-phenylhex-5-en-3-ol (1.25 mmol, 5.0 equiv). The reaction was stirred for 24 hours and afforded an orange crystalline solid (51 mg, 0.10 mmol, 37%).^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (s, 2H), 7.18 (dd, J = 8.1, 6.6 Hz, 2H), 7.15 – 7.08 (m, 2H), 6.95 (m, 5H), 6.91 – 6.88 (m, 2H), 6.77 (d, J = 8.8 Hz, 2H), 5.53 – 5.40 (m, 1H), 4.91 – 4.87 (m, 1H), 3.78 – 3.66 (m, 2H), 3.61 – 3.50 (m, 2H), 2.28 – 2.17 (m, 2H), 2.14 (s, 6H), 1.99 (m, 2H), 1.45 – 1.15 (m, 2H).



1-phenylhex-5-en-3-oxycarbonyl- cobalt 7,7'-dimethylsalen (3.42)

Prepared via redox neutral general procedure A using 130 mg **3.4•OTs** (0.25 mmol, 1.0 equiv), 81 mg Na_2CO_3 (0.75 mmol, 3.0 equiv) and 230 μL 1-phenylhex-5-en-3-ol (1.25 mmol, 5.0 equiv). The reaction was stirred for 24 hours and afforded an orange crystalline solid (49 mg, 0.08 mmol, 35%).^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51 (d, J = 8.1 Hz, 2H), 7.27 – 6.99 (m, 7H), 6.90 (t, J = 10.7 Hz, 4H), 6.40 (s, 2H), 5.38 (m, 1H), 4.84 (d, J = 13.7 Hz, 1H), 3.87 (m, 2H), 3.64 (m, 2H), 2.43 (s, 6H), 2.14 (s, 2H), 1.88 (s, 2H), 1.29 (m, 2H).



1-phenylhex-5-en-3-oxycarbonyl- cobalt-5-bromo-salen (3.43)

Prepared via redox neutral general procedure A using 140 mg **319•OTs** (0.25 mmol, 1.0 equiv), 81 mg Na_2CO_3 (0.75 mmol, 3.0 equiv) and 230 μL 1-phenylhex-5-en-3-ol (1.25 mmol, 5.0 equiv). The reaction was stirred for 24 hours and afforded an orange crystalline solid (21 mg, 0.03 mmol, 12%).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (s, 2H), 7.41 (dd, J = 10.2, 2.7 Hz, 2H), 7.31 – 7.06 (m, 7H), 7.03 – 6.87 (m, 2H), 6.81 (d, J = 9.0 Hz, 2H), 5.55 – 5.38 (m, 1H), 4.93 – 4.87 (m, 1H), 3.80 – 3.65 (m, 2H), 3.66 – 3.47 (m, 2H), 2.21 (m, 2H), 2.01 (m, 2H), 1.46 – 1.25 (m, 2H).

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Chapter 4 : Synthesis of Alkoxycarbonyl Cobalt Porphyrins and Irradiation of Alkoxycarbonyl Complexes for the Activation of Alcohols

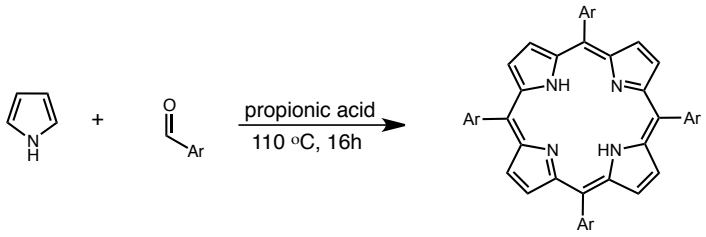
4.1 Introduction

While salen and salophen ligands have been the main focus of study of alkoxycarbonylcobalt complexes in the past, the robustness of porphyrins holds promise for enduring our photochemical reaction conditions without decomposition.[1,2] The synthesis and reactivity of *alkyl* cobalt porphyrin complexes have been studied,[3–5] including their bond dissociation energies[6,7] and applications in radical reactions, but much less is known about the *acyl* and *alkoxycarbonyl* complexes. Only one such derivative is reported, a methoxycarbonyl derivative, and it was utilized for the initiation of living radical polymerization by Fu and coworkers.[8] Development of a general synthesis of alkoxycarbonyl porphyrin complexes would facilitate further structure and reactivity studies. Herein, we describe the efficient synthesis of porphyrin-derived cobalt alkoxycarbonyl complexes and the study of the radical generation with visible light. This strategy enables the C–O bond activation of alcohols and alkyl radical generation with carbon dioxide as the only byproduct and establishes the fundamental processes for a cobalt-mediated C–O bond activation strategy.

4.2 Synthesis of Porphyrin Ligands

They synthesis of meso-substituted porphyrins has been extensively studied and optimized; however, due to their complex structures and propensity for polymerization

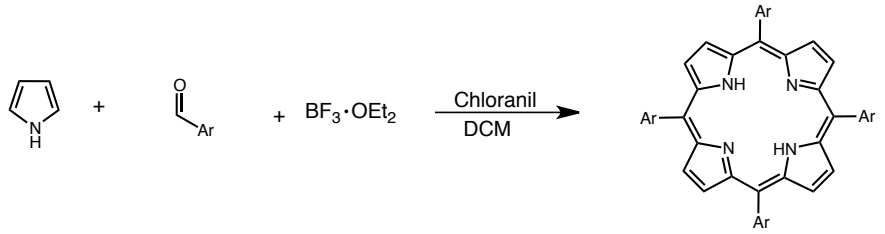
these steps are often still low yielding. Two chief one-pot syntheses are utilized, the first employing propionic acid as the solvent and reflux conditions (Table 4.1).[9] This method often produces inferior yields to the Lewis acid method, however, is ideal for workup and purification as it only requires filtration to isolate clean product. In our hands, the synthesis of 5,10,15,20-tetrakis(4-methoxyphenyl)porphyrin (TAP) **4.1** proceeded well under these conditions, however, the electron withdrawing 5,10,15,20-tetrakis(4-fluorophenyl)porphyrin (TFP) **4.2** formed in low yields and 5,10,15,20-tetrakis(2,4,6-trimethoxyphenyl)porphyrin (**4.3**) formation completely failed. The second method often employed, the Lindsey method, utilizes Lewis acids such as BF_3•OEt_2 (or protic acids such as TFA) to facilitate condensation and macrocyclization to the porphyrinogen and finally oxidation with strong benzoquinone oxidants such as DDQ and chloranil to yield the desired porphyrin.[10–12] This method can be used to synthesize porphyrins not obtainable by



Ar	Pdt	Yield
p-methoxyphenyl	**4.1**	50%
p-fluorophenyl	**4.2**	18%
2,4,6-trimethoxyphenyl	**4.3**	0%

Table 4.1 Synthesis of mesoporphyrins with propionic acid

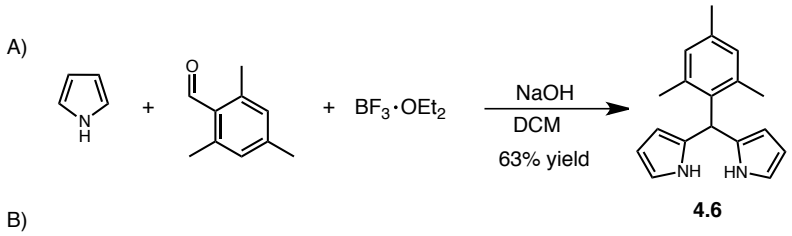
the propionic acid conditions; however, the workup is more tedious requiring quenching with base and column chromatography to obtain a pure product (Table 4.2).



Ar	Pdt	Yield
2,4,6-trimethoxyphenyl	**4.3**	35%
pentafluorophenyl	**4.4**	20%
Mesityl	**4.5**	10%
p-Fluorophenyl	**4.2**	0%

Table 4.2 One-pot synthesis of mesoporphyrins **4.2**-**4.5** with $BF_3 \bullet OEt_2$

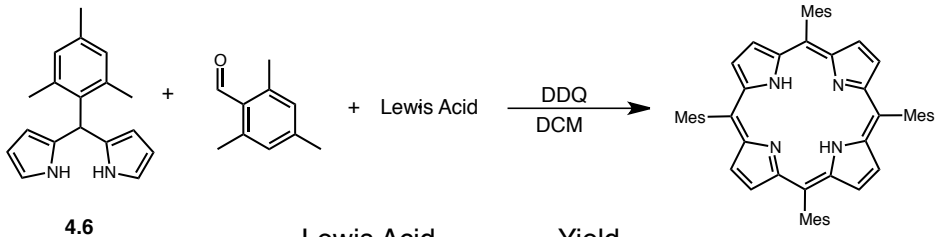
With this method, we were able to synthesize and isolate a good amount of porphyrin **4.3** while the previous method had no detectable product formation. Alternatively, we saw no TFP formation and only modest yields for the synthesis of 5,10,15,20 tetrakis(pentafluorophenyl)porphyrin **4.4** and 5,10,15,20 tetramesitylporphyrin (TMP) **4.5**. The one-pot methods can be very useful for quick formation of simple meso-



Ar	Pdt	Yield
p-Methoxy	**4.7**	50%
C_6F_5	**4.8**	40%

Table 4.3 Synthesis of dipyrromethanes **4.6**–**4.8**

substituted porphyrins but is not compatible with all benzaldehydes. In the case of mesitylaldehyde, the macrocycle formation was repeatedly low yielding or irreproducible, producing only the dimer or trimer condensation products even under forcing conditions, extended reaction times, and upon addition of 2,2-dimethoxypropane to scavenge water.[13] As such, we investigated the two-step method for porphyrin synthesis.[14] For this strategy, initial condensation of the benzaldehyde is achieved with pyrrole as the solvent and a Lewis acid to give the dipyrromethane products (Table 4.3). Dipyrromethane **4.6** was formed in good yields (63% yield) using BF_3•OEt_2 as the Lewis acid.[15] Based on literature precedent, dipyrromethane **4.7** and **4.8** were synthesized using TFA as the acid and proceeded in good yields.[16] All dipyrromethanes synthesized were purified by column chromatography and trituration with hexanes to give white or tan solids. After purification, a second condensation reaction with a 1:1 ratio of dipyrromethane and benzaldehyde with a Lewis acid achieves the desired porphyrin products (Table 4.4).



Lewis Acid	Yield
$BF_3 \cdot OEt_2$ (0.2 eq)	trace
$BF_3 \cdot OEt_2$ (0.4 eq)	10%
$BF_3 \cdot OEt_2$ (0.8 eq)	25%
$BF_3 \cdot OEt_2$ (1.2 eq)	15%
$InCl_3$	0%
TFA	0%

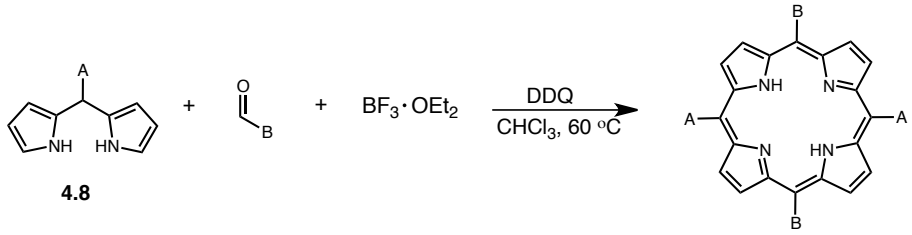
Table 4.4 Synthesis of porphyrin **4.5** from dipyrromethane **4.6**

TFA and $InCl_3$ were found to be ineffective, resulting in only dipyrromethane starting material after the reactions. When BF_3•OEt_2 was first investigated, only trace amounts of TMP were detected by mass spec, however, when equivalents of the Lewis acid

4.6 4.5

Figure 4.1 Optimal conditions for synthesis of porphyrin **4.5** from dipyrromethane **4.6**

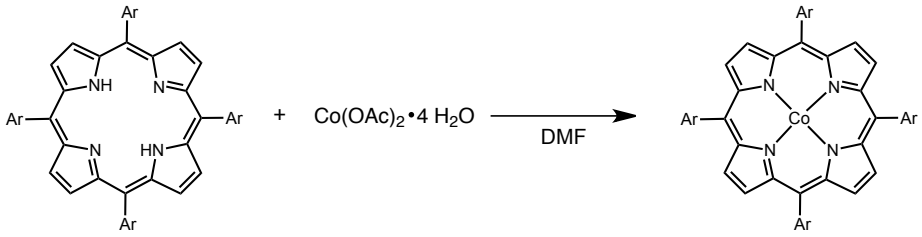
were increased, we observed an increase in yield, with the optimal amount of BF_3•OEt_2 determined to be at 0.8 equivalents. Final optimization was achieved by changing the solvent and reaction temperature from DCM and room temperature to $CHCl_3$ and 60 °C, respectively, to give the best yield of 31% (Figure 4.1). This method allowed us to make



A	B	Yield
C_6F_5	Ph	16%

Table 4.5 Synthesis of A:B porphyrin **4.9**

sterically hindered porphyrins as well as make mixed porphyrins (A:B meso porphyrins) (Table 4.5). Although only a modest yield was isolated, this method can be used to tune the porphyrin reactivity in a way that is not achievable using a one-pot process. This fine-



Ar	Pdt	Yield
C_6F_5	**4.10**	99%
Mesityl	**4.11**	96%
phenyl	**4.12**	91%
p-fluorophenyl	**4.13**	89%
2,4,6-trimethoxyphenyl	**4.14**	82%
p-methoxyphenyl	**4.15**	80%

Table 4.6 Synthesis of Co(II)porphyrin derivatives

tuning of the ligands could prove useful in future work. Incorporation of cobalt into the porphyrins was smoothly achieved by reflux with cobalt acetate and the porphyrin ligands (Table 4.6).[17] These reactions proceeded in excellent, often quantitative, yields and were easily isolated by silica gel column chromatography.

4.3 Synthesis of Alkoxycarbonyl Cobalt Porphyrin Complexes

After synthesis of these electronically diverse porphyrin ligands we turned our attention to the synthesis of alkoxycarbonyl cobalt porphyrin complexes with representative alcohols. Fu and co-workers have demonstrated the synthesis of a methoxycarbonyl cobalt (TMP) using methanol and silver(I) triflate under CO.[8] Unfortunately, this synthesis was only effective for simple alcohols (MeOH) and not effective with more complex alcohols in our hands, giving only undesired ether product **4.16** (Figure 4.2). Due to this undesired byproduct formation, we developed a method informed by studies of the carbonylation of salen and salophen cobalt complexes (Chapter

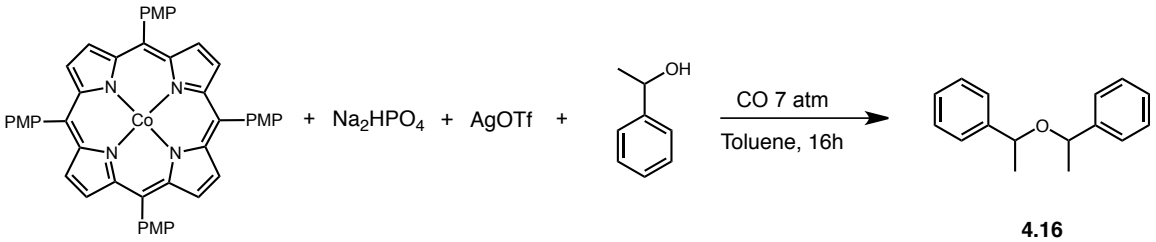
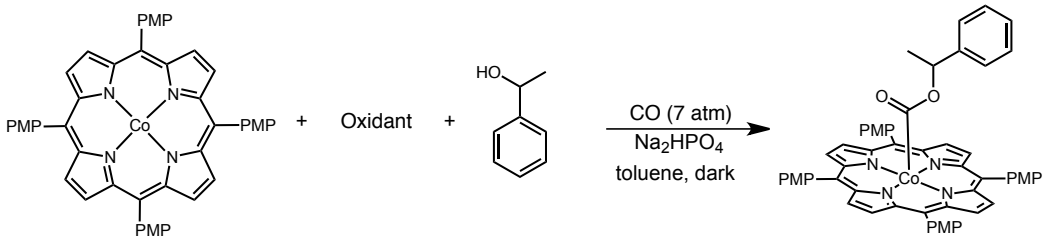


Figure 4.2 Ether byproduct **4.16** made under Fu and coworkers' carbonylation conditions

2 and 3). Both methods are quite general, tolerating a wide range of alcohols and ligand substitution patterns.[18] Unfortunately, cobalt porphyrin complexes have higher redox potentials[19] (more positive) compared to salen/salophen ligands, and when we first evaluated the oxidant required for this transformation, we found many inorganic oxidants and weaker benzoquinones ineffective (Table 4.7).



Oxidant	Yield*
DDQ	89%
$Na_2S_2O_8$	18%
$K_2S_2O_8$	16%
Oxone	7%
Chloranil	0%

* ^{1}H-NMR yield with internal standard

Table 4.7 Oxidative carbonylation of **4.15** with various alcohols. Reaction conditions: CoPorph (0.25 mmol), alcohol (1.25 mmol), DDQ (00.25 mmol), toluene (20 mL), 7 atm CO, rt

A strong oxidant such as DDQ was optimal for the *in-situ* oxidation without interfering with the carbonylation process. Once optimized conditions using 1 equiv of DDQ and 5 equiv of alcohol were developed, a representative set of alcohols were tested

to produced complexes **4.18-4.21** in good yields following purification by recrystallization from DCM and heptane (Table 4.8). This method was efficient for 1°, 2° and 3° alcohols.

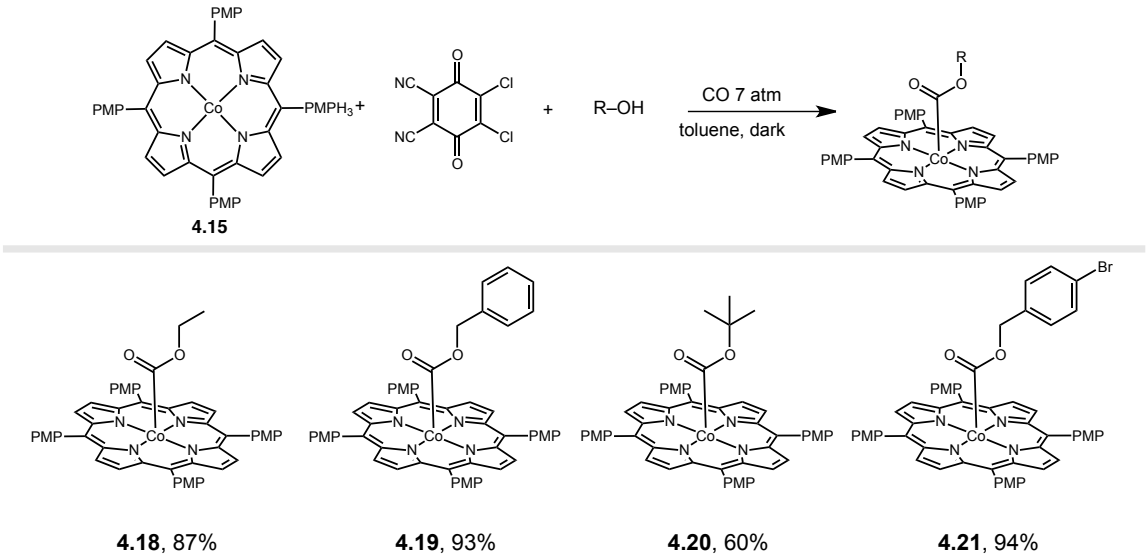
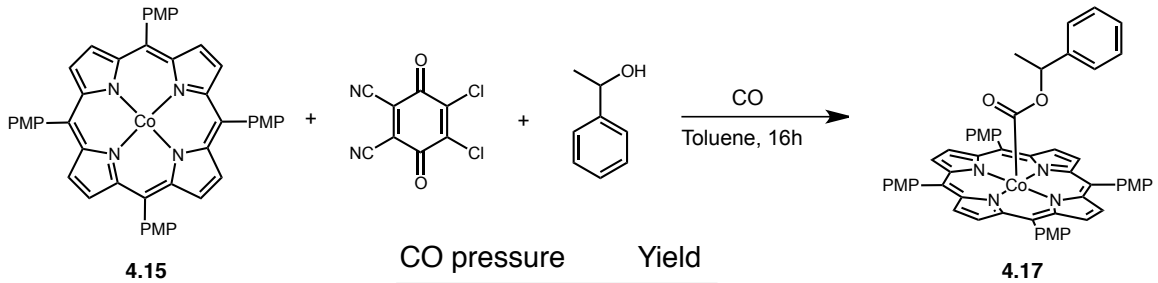


Table 4.8 Synthesis of alkoxycarbonyl cobalt complexes. Reaction conditions: Co(porph) (0.25 mmol), alcohol (1.25 mmol), DDQ (0.25 mmol), toluene (20 mL), 7 atm CO, rt

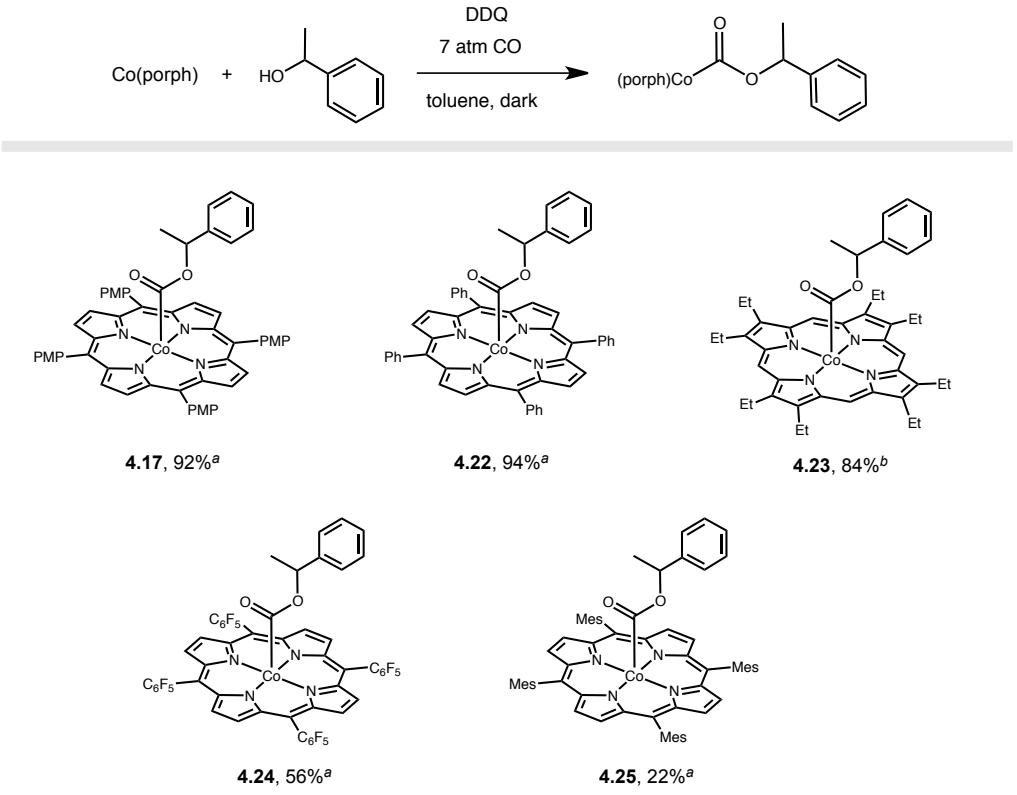
These complexes are air stable at room temperature for months, however, they are highly labile on either silica gel or alumina, resulting in decomposition to the Co(II) porphyrin starting material. Additionally, this system is more sensitive to changes in carbon monoxide pressures than other ligand systems, which will carbonylate under balloon CO pressure (Table 4.9). Under the standard reaction conditions established in Chapter 2, in



CO pressure	Yield
1 atm	37%
2 atm	70%
7 atm	92%

Table 4.9 Carbonylation of **4.15** with varying CO pressures

which carbon monoxide atmosphere was introduced by bubbling CO through the reaction solvent, no carbonylated product **4.17** was formed. However, when the reaction was properly degassed with three cycles of freeze-pump-thaw in a Schlenk tube before the addition of CO, a drastic increase in yield was observed. Additionally, as the pressure of carbon monoxide was increased from 1 to 2 to 7 atm we also observed a steady increase in yield after 16 h. This method of carbonylation was then tested on a wider range of porphyrin ligands with differing electronics (Table 4.10). Oxidation/carbonylation of 1-phenethanol with electron-rich porphyrin systems such as TAP, TPP and OEP gave



4.17, 92%[a] **4.22**, 94%[a] **4.23**, 84%[b]

4.24, 56%[a] **4.25**, 22%[a]

Table 4.10 Synthesis of 1-phenethyl alkoxycarbonyl cobalt complexes with porphyrin ligands of differing electronics. [a]Reaction conditions: Co(porph) (0.25 mmol), alcohol (1.25 mmol), DDQ (0.25 mmol), toluene (20 mL), 7 atm CO, rt. [b]Reaction conditions: Co(OEP) (0.25 mmol), alcohol (0.75 mmol), DDQ (0.25 mmol), toluene (15 mL), 7 atm CO, rt. Reduced amount of alcohol to facilitate isolation

excellent conversion to the corresponding complexes **4.17**, **4.22**, and **4.23**, respectively. The same transformation with the electron-deficient porphyrin TFP was achieved, albeit in lower yield. TMP was the least effective, likely due to the steric bulk. Overall, we have again developed a general method for the formation of alkoxycarbonyl cobalt porphyrin compounds.

4.4 Spectroscopic and Crystallographic Properties of Alkoxycarbonyl Cobalt Complexes

With the limited examples of alkoxycarbonyl cobalt porphyrin complexes to date, it was imperative to get spectroscopic and crystallographic data for our complexes to confirm their structure and properties. Beginning with ^{1}H NMR, we observed interesting upfield shifts due to the extended aromatic system of the porphyrin (Figure 4.3). The α-oxy C–H protons shifted upfield to 1.64 ppm and the β-oxy C–H at –0.74 ppm. These shifts are less pronounced than the alkyl equivalents **4.26**[20] and **4.27**[21] which are shifted significantly upfield, α-oxy C–H protons -3.46 – -3.71 ppm and β-oxy C–H at -4.97 ppm.

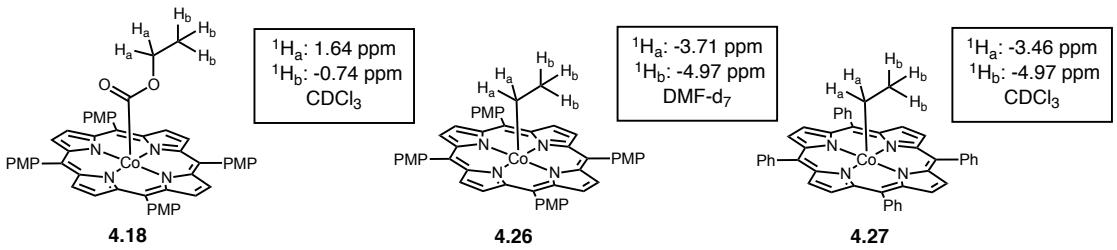


Figure 4.3 ^{1}H NMR shifts of alkoxycarbonyl complex **4.18** compared to alkyl counterparts **4.26** and **4.27**

In order to obtain detailed structural information, we carried out X-ray diffraction studies. Crystals of complex **4.17** were grown by slow diffusion of pentane into $CHCl_3$ resulting in long thin red crystals and were found to adopt a square pyramidal geometry

(Figure 4.4). This pentacoordinate configuration is commonly observed in similar porphyrin systems that contain acyl[22] and vinyl[23] substituents. The alkoxycarbonyl complex has a slightly shorter Co–C1 bond length compared to the acyl substituents (1.906 Å vs. 1.922-1.926 Å) and comparable Co–N bond lengths. The cobalt is displaced above the porphyrin plane toward the apical carbonyl group (C1), which is also observed in the other acyl and amine[24] examples but not in the instance with the apical alkene. This may result from a greater degree of back-bonding into the π* orbital of the alkoxycarbonyl and amine substituent that is less pronounced in the vinyl counterpart.

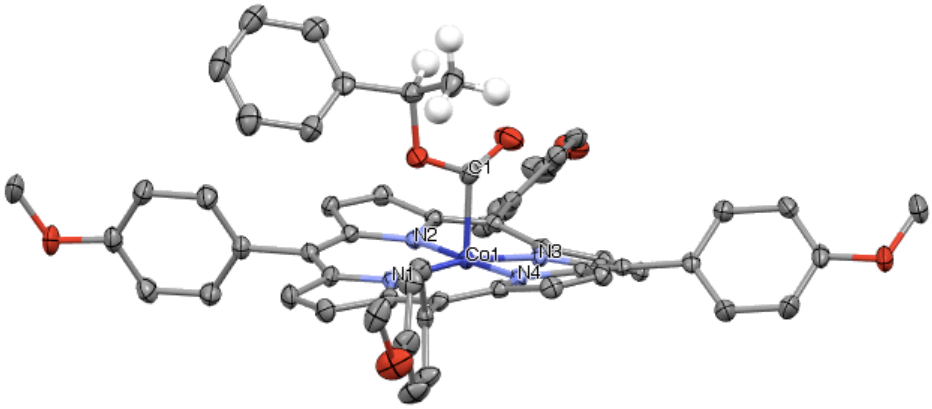


Figure 4.4 X-ray crystal structure of **4.17** with thermal ellipsoids at the 50% probability level. The compound crystallizes as a racemate; only one enantiomer is shown for clarity. Selected bond lengths (Å) and angles (deg): Co-C1 1.906(2), Co-N1 1.963(2), Co-N2 1.958(2), Co-N3 1.945(2), Co-N4 1.956(2); C1-Co-N3 95.45, C1-Co-N4 88.17, C1-Co-N1 96.45, C1-Co-N2 90.87, N3-Co-N4 89.79, N4-Co-N1 90.41, N3-Co-N2 89.76, N1-Co-N2 90.32.

With the structure of the alkoxycarbonyl complexes confirmed we further examined their spectroscopic characteristics. The UV-VIS absorption spectrum (Figure 4.6), obtained

by collaborator Antoine Juneau at the Université du Québec à Montréal (UQAM, Frenette group), exhibited a strong Soret band at 424 and Q band maximum at 540 nm.

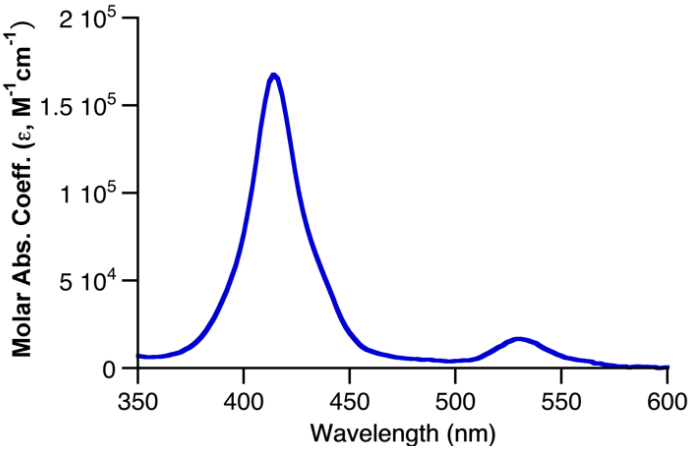


Figure 4.6 Absorption spectra of **4.17** in $CHCl_3$

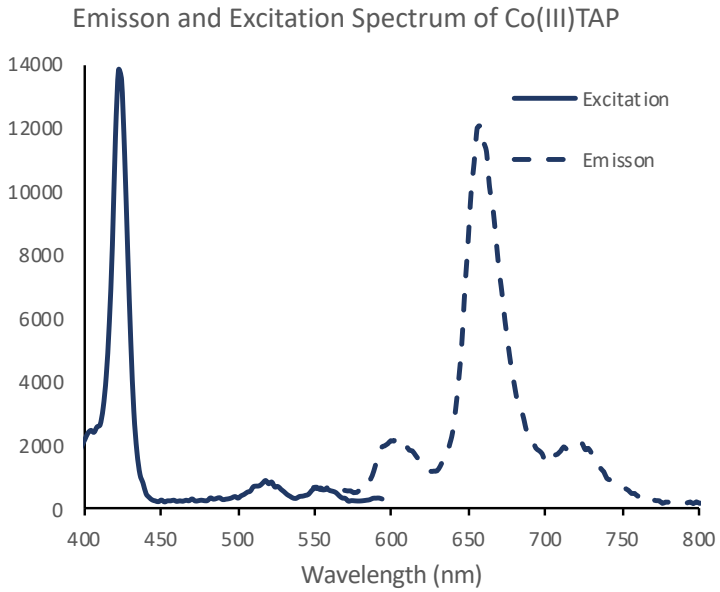


Figure 4.5 Emission and excitation spectra of compound **4.17** in $CHCl_3$

Excitation of the Soret band at 424 nm gave a strong emission at 660 nm (Figure 4.6, dashed line). Similarly, when the fluorescence of compound **4.17** was observed at 660 nm, the corresponding excitation spectrum (Figure 4.5, solid line) exhibited a strong response at 424 nm and minor absorbances at 526 and 558 nm.

4.5 Homolysis and TEMPO Trapping Reactions

We next examined the reactivity of the alkoxycarbonyl compounds under activation with visible light to determine if they retain behavior similar to vitamin B_{12} and their alkyl-cobalt analogs. Radical trapping experiments were performed using TEMPO as a radical

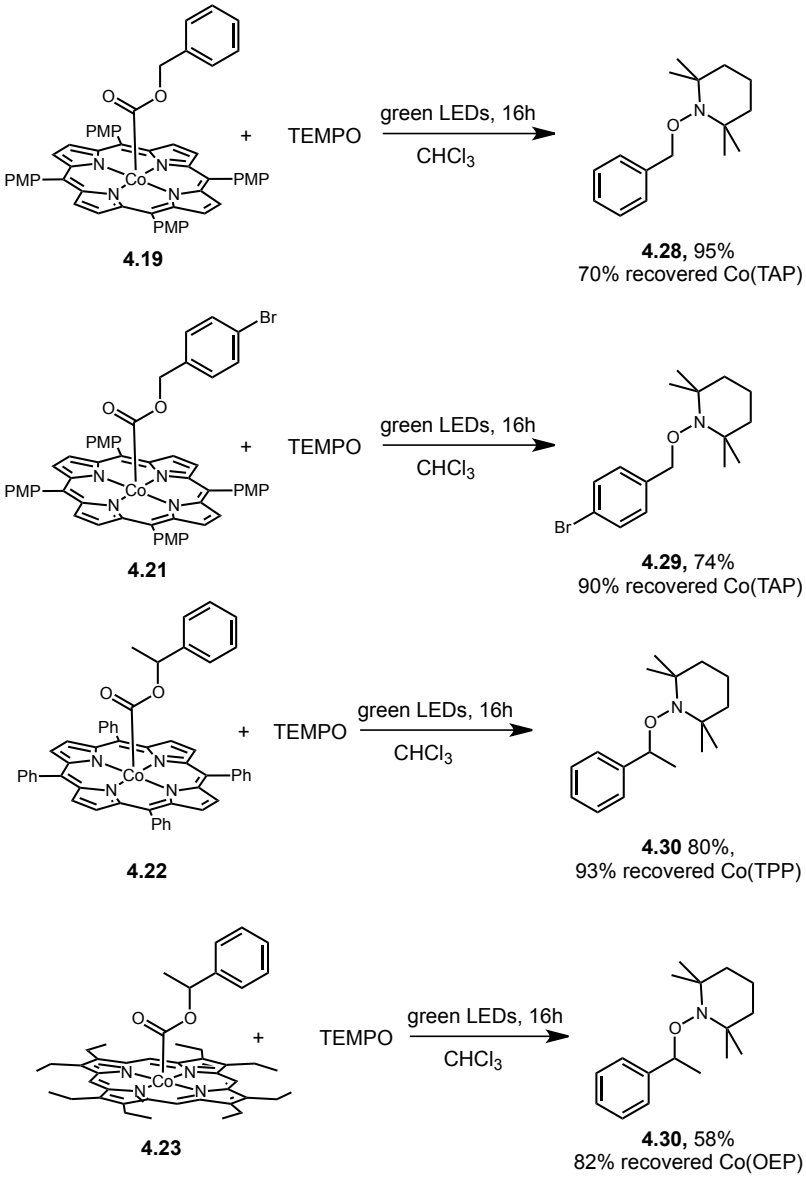
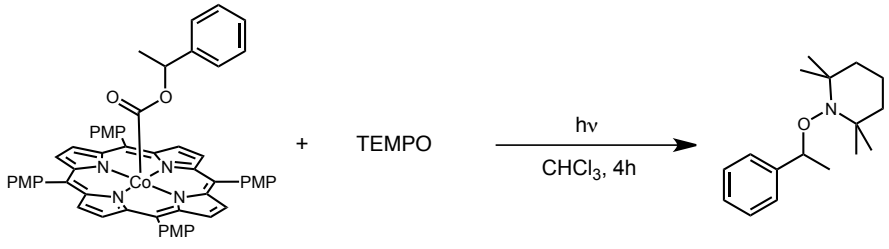


Figure 4.7 TEMPO trapping experiments Reaction conditions: **4.19**, **4.21**–**4.23** (0.02 mmol), TEMPO (0.04 mmol), CHCl3 (2 mL), rt.

trap and green light was used to homolyze the Co–C bond. The average energy of the green LED photons (~515 nm) is 55.5 kcal/mol; this energy is sufficient to cleave the C–Co bond, however, we can expect this bond to be thermally stable.

Based on studies by Newcomb and Pattenden, we expected to observe the decarboxylated products due to the rapid formation of stabilized benzylic radicals from the intermediate acyl radical.[25–28] Under our conditions, efficient homolysis and loss of CO_2 occurred and TEMPO adducts **4.28-4.30** were isolated in 58–95% yield; as expected only decarboxylated products were observed (Figure 4.7). Co(TAP), Co(TPP) and Co(OEP) were also isolated from these reactions, indicating that no major decomposition of the Co-porphyrin complexes took place under these reaction conditions. Interestingly, when the *p*-bromobenzyloxycarbonyl compound was subjected to irradiation conditions, the TEMPO isolated without loss of the bromine atom. This indicates the utility of this reaction as it has orthogonality to traditional radical chemistry and trapped product was metal catalysis reactions.



4.17 **4.30**

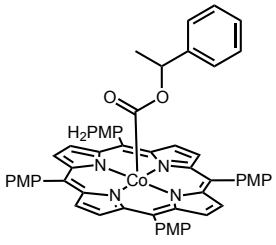
Light Source	Yield
450/550 nm	93%
390 nm	89%
456 nm	50%
440 nm	40%

Table 4.11 Study of homolysis via varying light sources

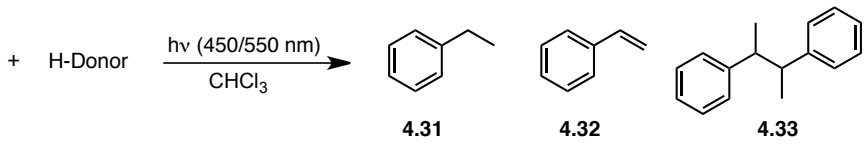
The light source for homolysis was tested and efficient radical generation could be achieved with a light source emitting at 390 nm or a mixture of 450 nm and 550 nm (Table 4.11). Green LEDs (510-520 nm) also gave full conversion, however took 16h, whereas the higher intensity Kessil LED lamps achieved the same conversion in 4h.[29] Some homolysis was observed with 440 and 456 nm light sources; however, these mismatched wavelengths were much less effective. This correlates well with the observed absorption spectra.

4.6 Hydrogen Atom Transfer Reactions

To further explore the utility of this strategy to deoxygenation, irradiation in the presence of a hydrogen atom donor was performed. We first studied some potential hydrogen atom donors (Table 4.12), based on appropriate BDEs and previous results (see Chapter 2).



4.17



4.31 4.32 4.33

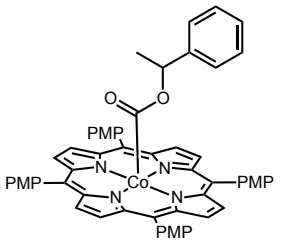
H-Donor	4.31	4.32	4.33
Dimethylthiophenol	48%	0%	0%
Tris(trimethylsilyl)silane	15%	0%	22%
1,3-Cyclohexadiene	5%	6%	20%
Trimethylhydroquinone	5%	22%	0%
-	5%	8%	20%

Table 4.12 Hydrogen atom donor screen

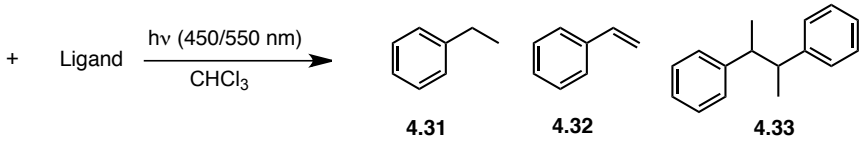
When no hydrogen atom donor was present, we observed small amounts of ethyl benzene and styrene, likely due to disproportionation of the intermediate radical,[30] and

predominantly dimerized product **4.33**. The formation of the dimer is consistent with a buildup of a high concentration of radical over time that can efficiently self-couple. 1,3-Cyclohexadiene was tested and was unproductive, giving yields similar to when no H-donor was present. Introduction of tris(trimethylsilyl)silane gave some **4.31** but still a majority of dimerized product **4.33**. Unsurprisingly, thiols and hydroquinones behaved similarly to previous studies, with thiols promoting ethyl benzene as the major product and hydroquinone favoring styrene and both preventing dimerization.

The addition of ligands has been shown to have a great effect on the selectivity between ethyl benzene and styrene (see Chapters 2 and 3). Again, we explored the effect of axial ligands with the porphyrin ligand system (Table 4.13). The addition of phosphine ligands has previously corresponded with an increase of ethyl benzene and overall yield. Triphenylphosphine appears to increase selectivity for ethyl benzene whereas tricylcohexylphosphine increases the total conversion of starting material to quantifiable product, however with loss in selectivity (i.e. more styrene). On the other hand, imidazoles



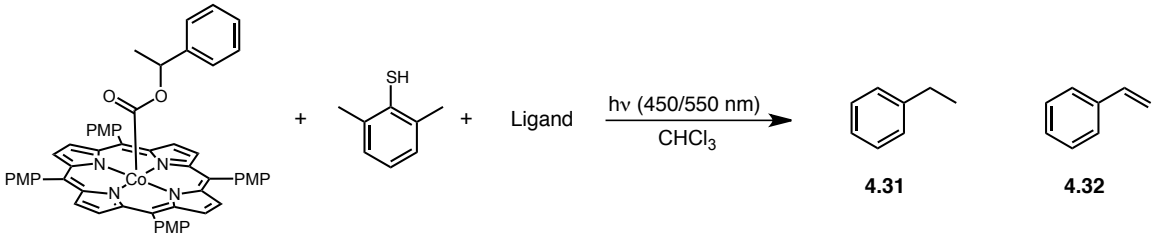
4.17



Ligand	4.31	4.32	4.33
PCy_3	26%	0%	20%
PPh_3	5%	0%	18%
none	9%	9%	26%
KCN	8%	8%	14%
Pyridine	3%	19%	30%
4-Phenylimidazole	0%	52%	0%
Benzimidazole	0%	55%	0%

Table 4.13 Ligand screen to test selectivity in formation of **4.31** and **4.32**

favored styrene formation, with both 4-phenylimiazole and benzimidazole reactions resulting in >50% yield **2.32** with no byproducts **2.31** or **2.33**. Further study into the phosphine ligands (Table 4.14) was undertaken in the presence of 2,6-dimethylthiophenol. Interestingly, when the mixed cyclohexyl-phenyl phosphines were tested, they follow the trend of selectivity, however, have a lower overall conversion than the non-mixedphosphines. Tris(2-furyl)phosphine and tri(o-tolyl)phosphine were also tested, demonstrating high selectivity for **4.31** but lower overall yield than triphenylphosphine.

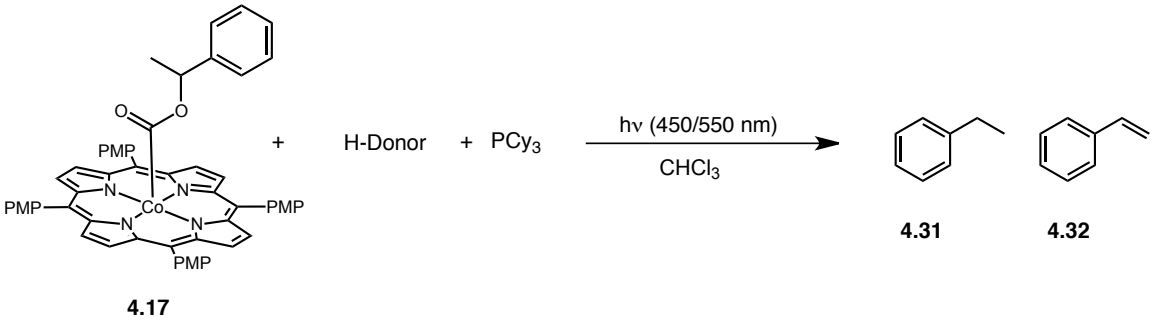


4.17 **4.31** **4.32**

Ligand	4.31	4.32
PPh_3	48%	0%
PCy_3	42%	21%
$P(furyl)_3$	37%	0%
$PCyPh_2$	34%	0%
$P(o\text{-}tolyl)_3$	32%	0%
PCy_2Ph	26%	13%

Table 4.14 Phosphine ligand study

Since tricyclohexylphosphine gave the highest conversion, it was use as the ligand in the evaluation of different thiols (Table 4.15). Both 2,4,6-triisopropylthiophenol and 2,6-dimethylthiophenol gave good conversion and a majority of ethylbenzene product (~46%). When using methyl thiosalicylate, the selectivity for ethylbenzene decreases and thiosalicylic acid showed no selectivity between **4.31** and **4.32**. Additionally, 2-methylpropane-2-thiol is not an efficient H-donor, producing only 15% **4.31** and favoring **4.32** at 40%. Finally, when benzenesulfinic acid was used no hydrogen atom donation was



4.17

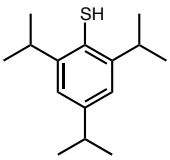
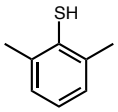
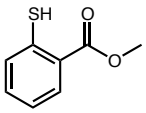
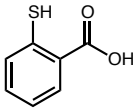
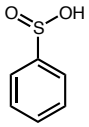
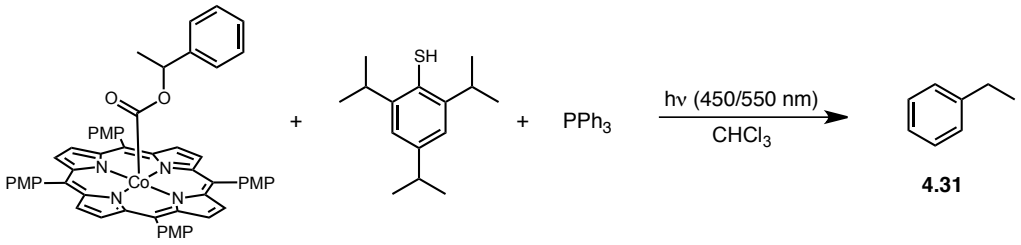
H-Donor	4.31	4.32
	47%	20%
	45%	21%
	42%	35%
	32%	31%
	15%	39%
	0%	17%

Table 4.15 Investigation of thiols as H-donors with PCy_3 as an axial ligand

observed, only modest amounts of eliminated product **4.32** were observed. Notably, in the presence of PCy_3 and any of the H-donors, no dimerized product was observed, even when low yields were observed.

As previously observed, thiols underwent rapid dimerization to the corresponding disulfide under our reaction conditions, which could be somewhat mitigated by increasing steric bulk at the ortho positions. However, even with an excess of hindered thiol, moderate yields were achieved along with full consumption of thiol to disulfide. Additionally, with increased reaction time formation of the thioether was observed from the reaction of the active radical with the disulfide. We explored Hantzsch ester and 1,3-cyclohexadiene as stoichiometric reducing agents to regenerate the thiol from the thiyl radical (Table 4.16). While cyclohexadiene was ineffective, with results ranging from 33% yield at 2 equivalents to 50% yield when used as the solvent, the addition of Hantzsch ester drastically increased the yield of ethyl benzene. Hantzsch ester was not effective by itself as an H-donor, however it was highly efficient at turning over the thiyl radical and allowed the H-atom donor to be reduced to sub-stoichiometric quantities, providing ethyl benzene in 86%



4.17 **4.31**

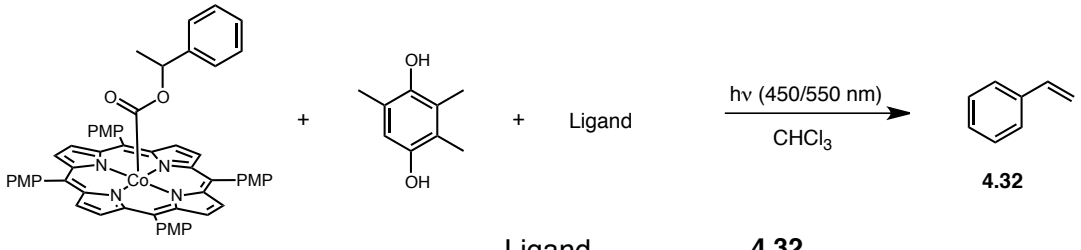
Additive	**4.31**
-	42%
1,3-cyclohexadiene	33%
Hantzsch ester	93%

Thiol : Hantzsch ester	**4.31**
2 : 2	88%
1 : 2	84%
0.5 : 2	86%

Table 4.16 Introduction of H-donor additives to regenerate thiol species

yield.[31] When styrene was added to reactions with triisopropylthiol and Hantzsch ester some conversion to ethylbenzene was also observed. This indicates that in reactions with Hantzsch ester it is possible that some styrene might still be produced but it is rapidly converted to ethylbenzene, conceivably by transfer hydrogenation.[32]

Achieving this transformation in excellent yield and selectivity, we were interested to see if we could attain the same yield and selectivity forming styrene (Table 4.17). Referring to conditions previously observed to favor styrene (imidazoles and trimethylhydroquinone), we were able to achieve styrene in admirable yields with no ethylbenzene or dimerized byproducts. As expected, trimethylhydroquinone without ligand already favors formation of **4.32** over **4.31** and **4.33** and the yield is enhanced by addition of imidazole ligands. Benzimidazole was found to produce styrene in excellent yields (91%) with good yields achieved with both imidazole and 4-phenylimidazole, 69% and 78% yields, respectively. These studies demonstrate that decarboxylation and radical trapping can be achieved with these complexes under mild conditions and can be easily tuned by changing axial ligands and H-donors.



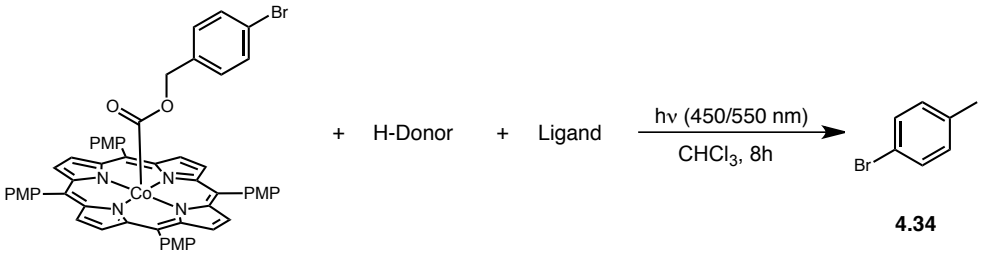
4.17

Ligand	**4.32**
Benzimidazole	91%
4-Phenylimidazole	78%
Imidazole	69%
None	40%

Table 4.17 Ligand optimization for styrene production upon homolysis of **4.17**

4.7 Homolysis-Decarboxylation to form *p*-Bromotoluene

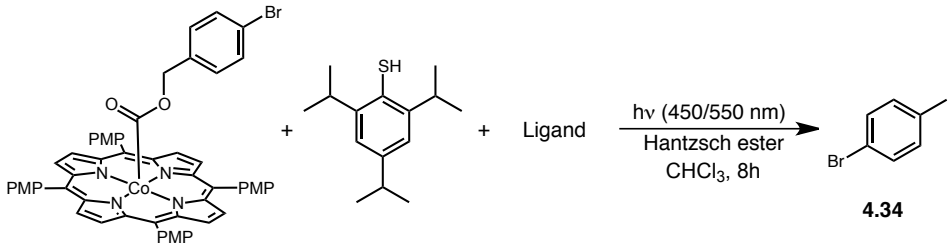
From our studies with 1-phenylethanol, we achieved selectivity in product formation (ethylbenzene vs styrene) and decided to look at another alcohol to see the applicability of this method. We resolved to investigate the irradiation of **4.21** to synthesize *p*-bromotoluene because the reaction would proceed via a similar benzylic radical to the previously studied alcohol but without option of β-hydrogen elimination, potentially simplifying the outcome. As shown in Table 4.18, triisopropylthiophenol was studied as a hydrogen atom donor for the formation of **4.34**. The choice of H-donor was based on the previous results of HAT that we observed under our optimal reaction conditions with 1-phenylethanol. In the absence of ligand, we observed modest yields of bromotoluene (21%). The addition of PPh_3 actually decreased the yield slightly, however when employing a combination of PPh_3, triisopropylthiophenol and Hantzsch ester we again see a good yield of desired product **4.34**. Unsurprisingly, when investigating conditions which favor β-



H-Donor	Ligand	Yield
Triisopropylthiophenol	–	21%
Triisopropylthiophenol	PPh_3	15%
Triisopropylthiophenol/Hantzsch ester	PPh_3	50%
Trimethylhydroquinone	Benzimidazole	–

Table 4.18 Irradiation of **4.21** to form **4.34**

hydrogen elimination, trimethyl hydroquinone and benzimidazole, we observed no desired product.



Ligand	Yield
$P(furyl)_3$	41%
Benzimidazole	37%
4-Phenylimidazole	36%
Pyridine	32%
–	31%
KCN	29%
PCy_3	27%

Table 4.19 Ligand screen for formation of **4.34**

With the slight drop in yield when employing PPh_3, a further investigation into ligands for this system was studied (Table 4.19). Predictably, PPh_3 and $P(furyl)_3$ increase the yield of bromotoluene (by analogy to 1-phenylethanol reactions), however, intriguingly benzimidazole and 4-phenylimidazole also increased the yield of desired product compared to no ligand. As these imidazole ligands had previously favored eliminated products, we had predicted that they would cause a lower yield of **4.34** compared with no ligand. Interestingly, regardless of what ligand was examined, the formation of bromotoluene was achieved in moderate to good yields. Furthermore, under all conditions tested bromotoluene was the only product detected and no toluene was observed. This confirms that under our conditions bromine radical abstraction is not preferred, which makes this method complimentary to traditional radical reactions.

4.8 Giese Additions

Giese addition reactions of radicals derived from the homolysis of alkyl cobalt complexes have been reported by Pattenden and coworkers.[33–35] However, no yields were reported for these reactions, many reaction details were not provided and no examples of porphyrin complexes were reported. As previously discussed, (see Chapter 2) Giese additions might provide an elegant way to achieve catalytic turnover for our system. Unfortunately, efforts to achieve Giese additions of the ethyl ester acyl radical with Michael acceptors all failed in our hands (Figure 4.8). No desired product or expected byproducts were observed under any reaction conditions tested, including with the addition of various H-donors and ligands, though full consumption of the Michael acceptor was always observed by GC. It is plausible that we are simply polymerizing the Michael acceptor under our reaction conditions. More studies are needed to optimize these reaction conditions and prevent polymerization of the Michael acceptor.

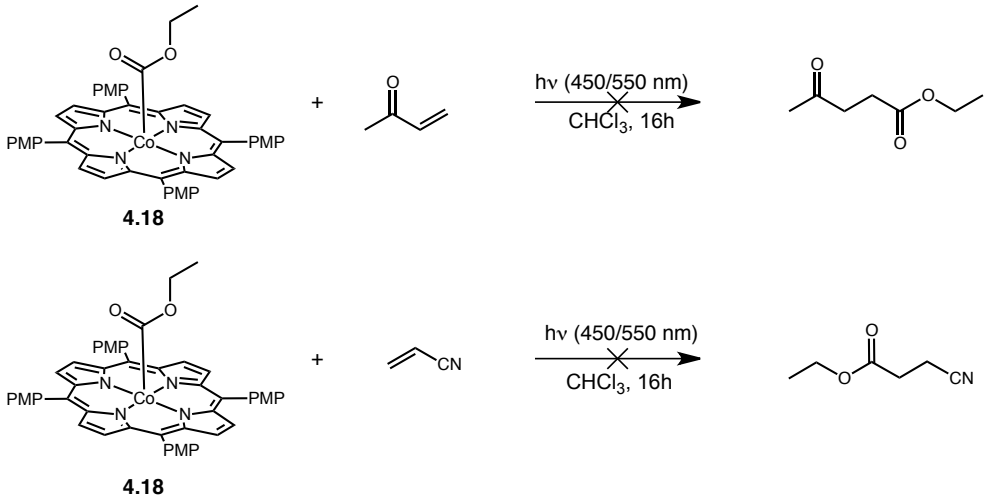
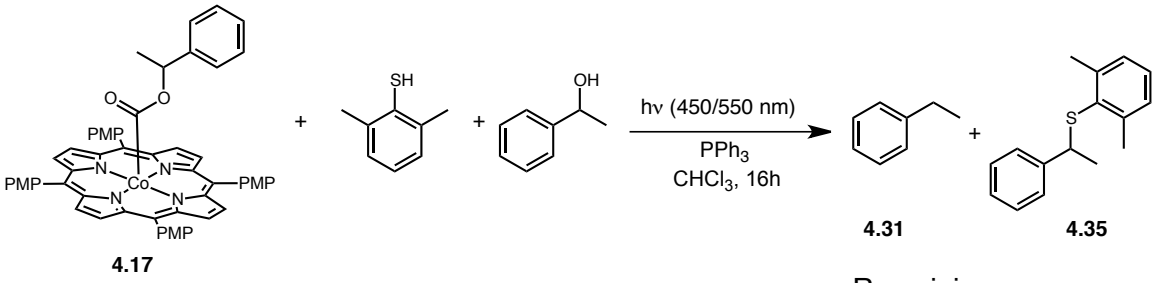


Figure 4.8 Attempted Giese reactions from **4.18**

4.9 Attempted Catalytic Reactions from Alkoxycarbonyl Co(III)TAP

Initial studies converting these stoichiometric transformations into a catalytic system focused on mitigating any incompatibilities between these stoichiometric reactions when adapting the reaction to a one-pot process. First, the addition of excess alcohol was tested to see if the presence of alcohols inhibited H-atom donation (Table 4.20). When comparing 0, 5 and 10 equivalents of 1-phenethylalcohol, there is no inhibition of ethylbenzene formation but an observable decrease in the formation of the thioether byproduct. Unsurprisingly, there was no significant consumption of 1-phenethylacohol under these reaction conditions as there was no carbon monoxide for carbonylation to proceed.

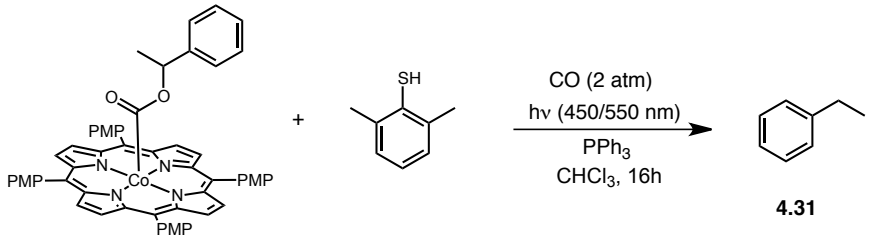


4.17 **4.31** **4.35**

Alcohol	**4.31**	**4.35**	Remaining Alcohol
0 equiv	40%	40%	0%
5 equiv	35%	33%	460%
10 equiv	36%	16%	956%

Table 4.20 Addition of 1-phenethylalcohol to irradiation reactions

Next, the change in atmosphere from nitrogen to carbon monoxide was tested (Table 4.21). With the pentacoordinate alkoxycarbonyl porphyrin complex there is potential for carbon monoxide to act as an axial ligand, and the addition of axial ligands has had an immense effect on reactivity in our previous studies. Comparing nitrogen to carbon monoxide atmospheres, in the absence of other ligands, a small reduction in



4.17 **4.31**

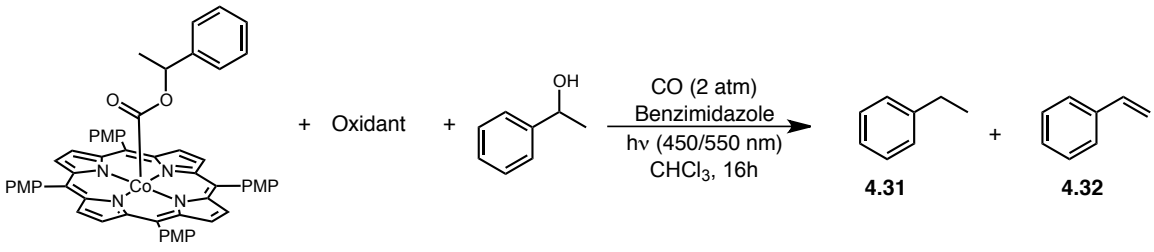
Atmosphere	Ligand	**4.31**
N_2	–	40%
CO	–	31%
N_2	PPh_3	43%
CO	PPh_3	41%

Table 4.21 Homolysis of **4.17** with N_2 and CO atmospheres

ethylbenzene formation was observed when CO was used. When triphenylphosphine was added into the reaction vessel the change in ethylbenzene between nitrogen and carbon monoxide was negligible. This suggests that carbon monoxide is likely coordinating to some extent and that the use of ligands in the catalytic system could mitigate any negative effects of coordination. Furthermore, it suggests that ligands like triphenylphosphine bind favorably to the cobalt porphyrin complex over carbon monoxide. Knowing that the presence of alcohol and carbon monoxide does not inhibit this reaction, we focused on turnover of Co(II) to Co(III).

In order to achieve turnover in this reaction, we need to re-oxidize the Co(II)(por) that is produced during homolysis. Preliminary studies for re-oxidation employed inorganic oxidants that had been successful in the original oxidation-carbonylation studies. With a 20 mol% loading of **4.17** and 5 equivalents of inorganic oxidant under irradiation conditions (2 atm CO, Schlenk tube, light), the formation of ethylbenzene and styrene and the consumption of 1-phenethylalcohol were tracked by GC (Table 4.22). When oxidants

were employed, even in the absence of H-donors or ligands, styrene was exclusively formed.

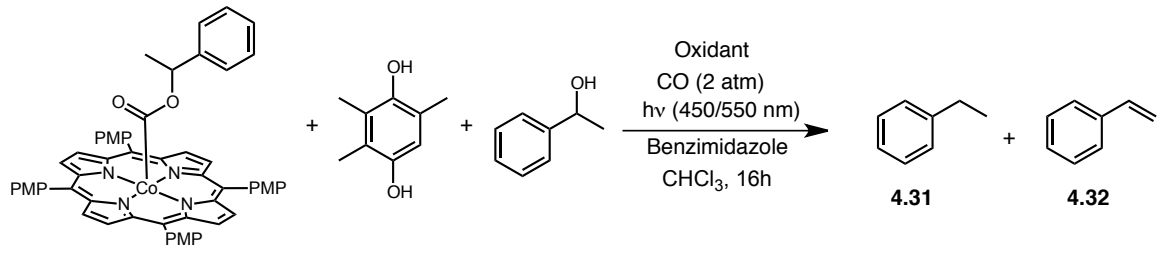


4.17

Oxidant	4.31	4.32	Remaining Alcohol
Oxone	0%	12%	113%
$K_2S_2O_8$	0%	12%	102%
$(NH_4)_2S_2O_8$	0%	7%	100%
$Na_2S_2O_8$	0%	0%	105%
–	0%	0%	113%

Table 4.22 Examination of inorganic oxidants for catalytic turnover

However, no 1-phenethylalcohol was consumed with any of these oxidants, suggesting that the Co(II) was not re-oxidized. Since styrene was favored under oxidative conditions, trimethylhydroquinone and benzimidazole were examined to see if higher conversion could be achieved (Table 4.23). When no oxidant is used, a mixture of



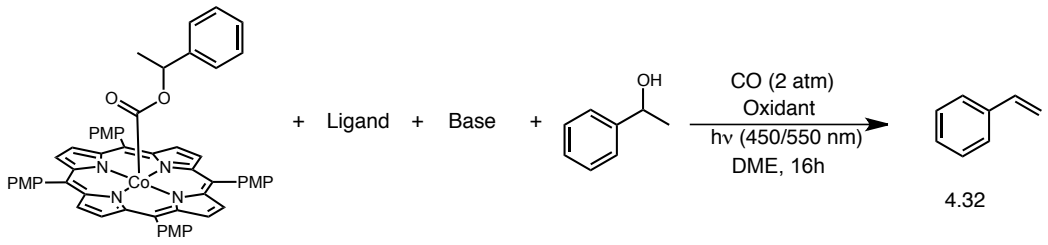
4.17

Oxidant	4.31	4.32	Remaining Alcohol
–	3%	12%	80%
Oxone	0%	11%	100%
DDQ	0%	6%	100%
$Na_2S_2O_8$	2%	0%	80%
$K_2S_2O_8$	2%	2%	100%

Table 4.23 Study of inorganic oxidants for catalytic turnover under styrene formation conditions

ethylbenzene and styrene was observed with marginal consumption of 1-phenethylalcohol. DDQ appears to inhibit styrene formation and under these conditions the remaining inorganic oxidants result in ethylbenzene as the major product with minimal to no consumption of alcohol. Notably, at the completion of these reactions there is no hydroquinone observed by GC. It is probable that the oxidants are oxidizing trimethylhydroquinone to the corresponding quinone, thus consuming oxidant faster than it could be used for oxidation/carbonylation and preventing hydroquinone from being used as intended in the reaction. With this in mind, we then repeated the reaction without the addition of hydroquinone. We see almost identical results in the presence or absence of trimethylhydroquinone.

Next, we probed this reaction with different ligands in combination with a few bases commonly used in photocatalysis reactions (Table 4.24). Taking the best oxidants from earlier studies, $K_2S_2O_8$ and Oxone were tested. Both oxidants followed similar trends with ligand and base combinations, with DMAP forming the least amount of styrene and a high amount of excess 1-phenylethanol. When using cyanide as a ligand (KCN), styrene formation was slightly improved (0% to ~7%). The yield was unchanged when adding potassium carbonate as a base but was again slightly improved using cesium carbonate. However, in all cases no significant conversion to styrene and no turnover was ever observed. Finally, the reaction with $K_2S_2O_8$ and DMAP was repeated in a Fisher Porter reaction vessel which allowed 7 atm of carbon monoxide to be used instead of 2 atm. The



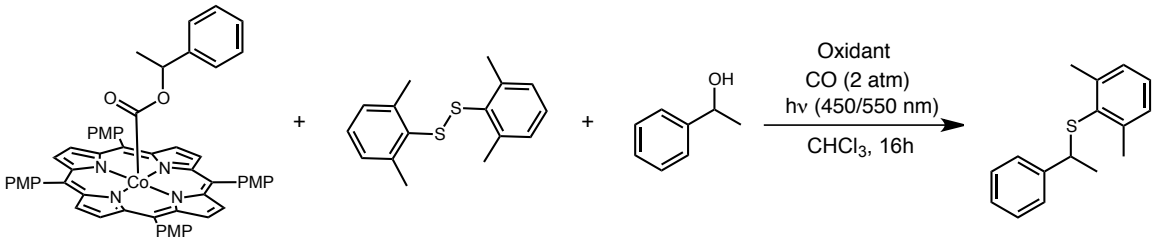
Oxidant	Ligand	Base	4.32	Remaining Alcohol
$K_2S_2O_8$	DMAP	–	0%	123%
$K_2S_2O_8$	KCN	–	6%	104%
$K_2S_2O_8$	KCN	$CsCO_3$	13%	114%
$K_2S_2O_8$	KCN	K_2CO_3	8%	108%
Oxone	DMAP	–	3%	106%
Oxone	KCN	–	8%	116%
Oxone	KCN	$CsCO_3$	11%	100%
Oxone	KCN	K_2CO_3	8%	108%

Table 4.24 Investigation of different ligand and base combinations for catalytic turnover

intention of this reaction was to facilitate carbonylation/turnover with increased CO pressure but still maintain a vessel made of glass so light could be utilized for homolysis. The reaction in the Fisher Porter vessel saw a mild increase in styrene formation from 0% to 4% and no increase in 1-phenethyl alcohol. The resistance to decarbonylation with the increased CO pressure is promising, however, still no consumption of 1-phenethyl alcohol was observed and thus no turnover occurred.

The incompatibilities of hydroquinones and thiols with oxidants in these catalytic reactions were initially disheartening and led us to simplify the reaction conditions to prevent such conflicts. Thus, we investigated the formation of thioether **4.35** under catalytic conditions as we anticipated that an oxidant would produce the disulfide readily from the thiol or any thiyl radical formed (Table 4.25, A). Conversion to thioether **4.35** was achieved efficiently when no oxidant or inorganic oxidants were used, however no turnover was observed (20% theoretical yield with no turnover). This is not exceedingly surprising as

inorganic oxidants have not been efficient for oxidation of porphyrins. Interestingly, when DDQ was used no thioether was observed, and only a modest amount of styrene was



4.17 **4.35**

(A)

Oxidant	**4.32**	**4.35**
–	0%	15%
$K_2S_2O_8$	0%	15%
Oxone	0%	15%
DDQ	4%	0%

(B)

Oxidant	**4.32**	**4.35**
Methylbenzoquinone	0%	0%
Tetrabromobenzoquinone	2%	0%
2,5-Dihydroxy-1,4-benzoquinone	0%	10%
Tetramethylbenzoquinone	1%	13%

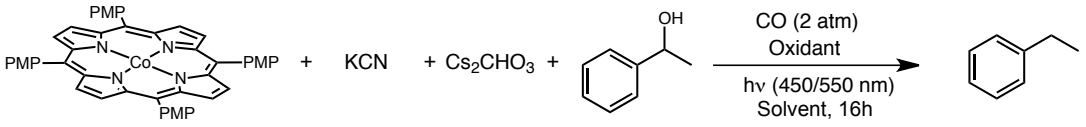
Table 4.25 Catalytic reaction conditions to form thioether **4.35**. 20 mol % **4.17**, 5 equiv disulfide, and 1 equiv 1-phenylethanol

detected. Since inorganic oxidants seem to have no effect and DDQ is too strong of an oxidant, numerous other quinones were tested (Table 4.25, B). The highly tunable nature of quinones make them promising to find an oxidant strong enough to oxidize Co(II)TAP without sabotaging the overall reaction. However, after many quinones were tested, no conditions were found to promote turn over.

4.10 Catalytic Attempts from Co(II)porphyrin

Due to the issues with turnover, we decided to probe the reaction further to determine where the incompatibilities originated. Starting with a 20 mol% loading of

Co(II)TAP, we ran a one-pot reaction with oxidant, ligand, alcohol and light that stirred for 16 h (Table 4.26).



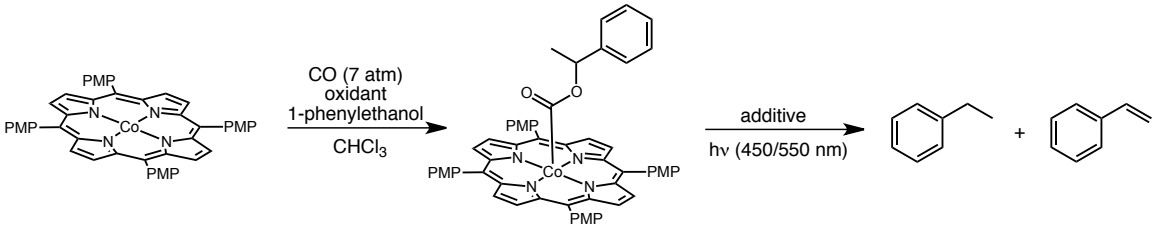
4.15 **4.31**

Solvent	Oxidant	Base	**4.31**	1-phenethylalcohol
DCM	$K_2S_2O_8$	1 equiv	0%	84%
DCM	$K_2S_2O_8$	–	0%	75%
Toluene	$K_2S_2O_8$	1 equiv	2%	80%
Toluene	$K_2S_2O_8$	–	2%	80%
DCM	Oxone	1 equiv	0%	85%
DCM	Oxone	–	0%	95%
Toluene	Oxone	1 equiv	1%	77%
Toluene	Oxone	–	2%	96%

Table 4.26 One-pot carbonylation-irradiation reactions. 20 mol% Co(TAP), 2 equiv KCN, 2 equiv Cs_2CO_3, 1 equiv 1-phenylethanol

These reactions were run in Schlenk tubes as they can be pressurized to 2 atm CO and light can readily penetrate the reaction mixture. These one-pot reactions were run with 20 mol% CoTAP and yields are based off of 1-phenethylalcohol as the limiting reagent. Using the best inorganic oxidants from previous experiments, each reaction was run for 16 h stirring in direct light from Kessel's LED lamps. None of the reactions, regardless of oxidant, solvent, ligand or base gave more than trace amounts of ethylbenzene or styrene. Up to 25% of the 1-phenethylalcohol was consumed in these reactions, unfortunately, we could not identify if oxidation/carbonylation occurred or that side reactions are transpiring. However, as a one-pot reaction, we still see an inhibition of product formation when all components are added into the reaction mixture.

To further probe this incompatibility, we investigated this reaction in tandem rather than one-pot (Table 4.27). In these reactions, carbonylation was achieved by the addition of CoTAP, oxidant, alcohol and $CHCl_3$ in a 20 mL vial in the pressure vessel charged to 7 atm. The goal was to increase CO pressure and thus increase carbonylation under sub-optimal conditions ($CHCl_3$ vs toluene and $K_2S_2O_8$ vs DDQ). Carbonylation was achieved for reactions with DDQ and, to a lesser extent, $K_2S_2O_8$. Upon completion, these reaction mixtures were transferred into Schlenk tubes and the H-donor was added. Reaction mixtures were then fully degassed with three cycles of freeze-pump-thaw and irradiated with high intensity LED lamps for 16 h. No purification was performed between carbonylation and irradiation and the H-donor was added after carbonylation to alleviate any impediment to carbonylation. However, even in a tandem reaction system, no ethylbenzene or styrene was observed. In the case of reactions using DDQ, while carbonylation is efficient, DDQ (or its byproduct) clearly inhibits irradiation reactions.



4.15 4.17 4.31 4.32

Oxidant	Additive	4.31/4.32	1-phenethylalcohol
DDQ	–	0%	87%
DDQ	Trimethylhydroquinone	0%	93%
DDQ	Triisopropylthiophenol	0%	100%
DDQ	Triisopropylthiophenol/Hantzsch	0%	96%
$K_2S_2O_8$	Trimethylhydroquinone	0%	92%
$K_2S_2O_8$	Triisopropylthiophenol	0%	100%
$K_2S_2O_8$	Triisopropylthiophenol/Hantzsch	0%	84%

Table 4.27 Tandem carbonylation-irradiation reactions. 20 mol % Co(TAP), 5 equiv oxidant, 1 equiv 1-phenylethanol and 2 equiv additive

When $K_2S_2O_8$ is utilized it is likely that not enough carbonylated product is formed in the initial transformation to give appreciable homolysis products. Ultimately, the combination of irradiation reaction conditions with oxidants appears to be incompatible and we must investigate different oxidants.

4.11 Dual Catalytic System

While debating a suitable oxidant for these transformations, work by Ritter and coworkers explored a dual catalytic cycle between an iridium photocatalyst and cobaloxime.[36] With their *Nature* paper as inspiration, we explored a dual catalytic system using a photocatalyst and the alkoxycarbonyl cobalt porphyrin complexes. We envision our Co(III)TAP carbonylating in the presence of our desired alcohol, homolyzing using green light, decarboxylating and getting reduced by a hydrogen atom donor, as we previously proposed (Figure 4.9). Now, we also anticipate an iridium photocatalyst excited by a visible or near UV light source will be oxidizing enough to oxidize Co(II)TAP to Co(III)TAP, regenerating our active cobalt species. Additionally, [Ir^{II}] could reduce the resulting H-donor radical, ultimately regenerating the iridium catalyst. Finally, the reduced H-donor can be re-protonated by the HX formed from carbonylation. This elegant method would be catalytic in cobalt, iridium and H-donor with the only byproduct being carbon dioxide.

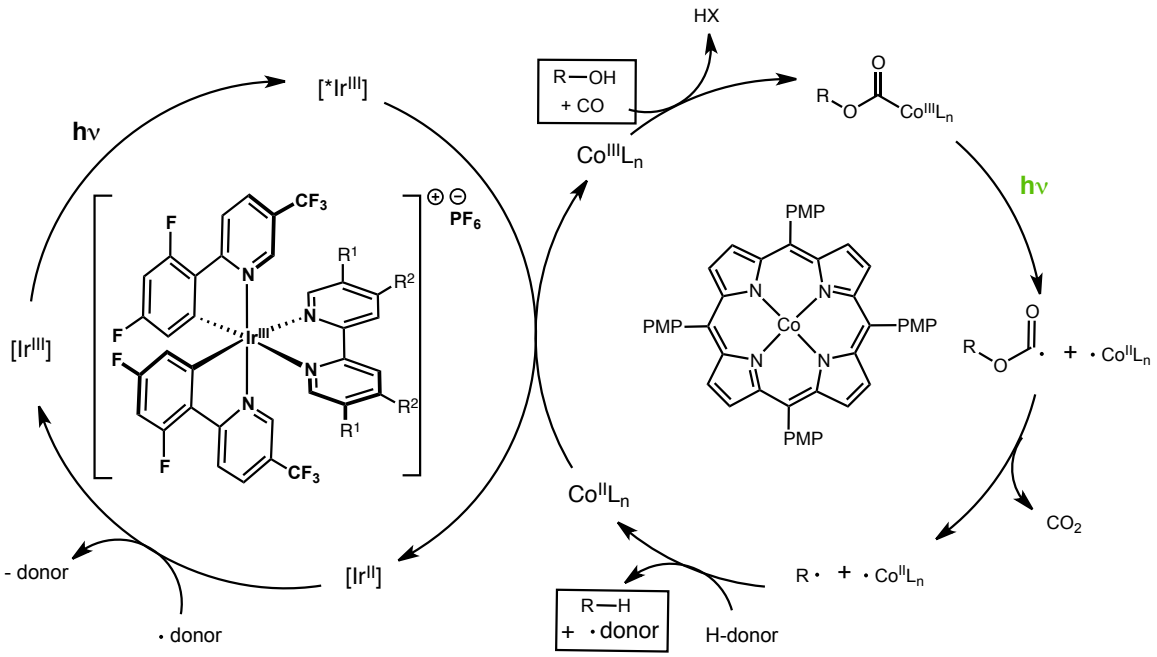
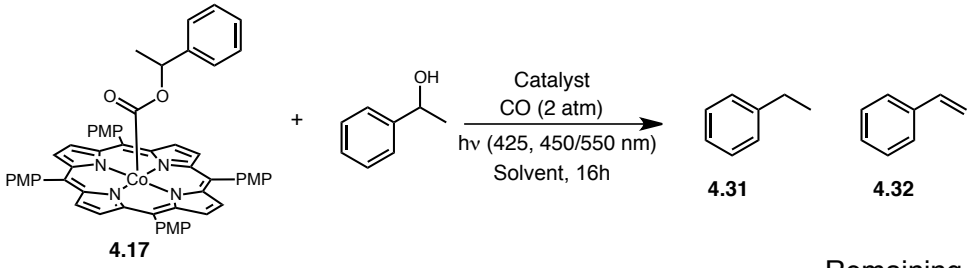


Figure 4.9 Proposed dual catalytic cycle with cobalt porphyrin and iridium photocatalyst. R^1 = H, R^2 = *tert*-butyl (**4.36**) or R^1 = CF_3, R^2 = H (**4.37**)

Preliminary studies of this dual catalytic system tested various highly oxidizing ruthenium and iridium photocatalysts.[37] The iridium photocatalysts were prepared by Abigail Feceu: photocatalyst **4.36**: R^1 = H, R^2 = *tert*-butyl and **4.37**: R^1 = CF_3, R^2 = H. This system required a slightly more complex set up as these photocatalysts are excited at different wavelengths than our cobalt catalyst. We employed both Kessel lamps that emit 425 nm light, which is ideal for ruthenium and iridium, and the 450/550 nm lamp which is optimal for cobalt–carbon homolysis (Table 4.28). Our initial studies produced minimal desired product **4.31** or **4.32**. Unsurprisingly, slightly more eliminated product **4.32** was observed, as the photocatalysts should act as an oxidant. The low yields and minimal alcohol consumption under these reaction conditions caused us to investigate the effect of ligands on this system (Table 4.29).

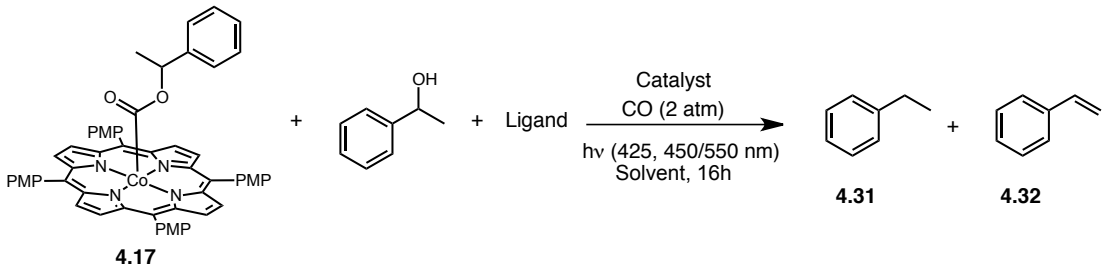
With PCy_3 as ligand, again, only trace amounts of desired product were formed and, in most cases, it appears **4.17** has decomposed into 1-phenylethanol. Using KCN and DMAP as ligands did not increase the formation of the desired product, however they did prevent the additional alcohol formation. Ultimately, the iridium catalysts again seem to



Catalyst	Solvent	**4.31**	**4.32**	Remaining Alcohol
$Ru(bpy)_2(PF_6)_2$	DCM	0%	8%	80%
$Ru(bpy)_2(PF_6)_2$	DME	0%	7%	100%
$Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$	DCM	0%	1%	100%
$Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$	DME	5%	0%	100%
$Ir(dF(CF_3)ppy)_2(dCF_3bpy)PF_6$	DCM	0%	7%	92%
$Ir(dF(CF_3)ppy)_2(dCF_3bpy)PF_6$	DME	1%	8%	100%

Table 4.28 Initial studies of the dual catalytic system with different photocatalysts

inhibit product formation although catalyst **4.37** does appear to have some preferential formation for styrene. Further study into conditions and variations of the iridium catalysts would be beneficial.



4.17 **4.31** **4.32**

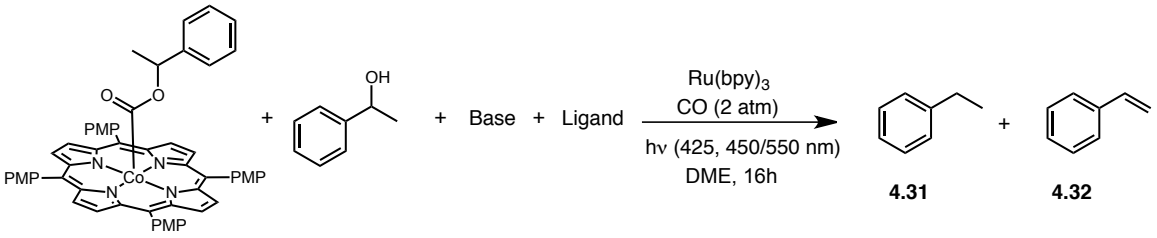
Catalyst	Ligand	Solvent	**4.31**	**4.32**	Remaining Alcohol
$Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$	PCy_3	DCM	0%	1%	127%
$Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$	PCy_3	DME	4%	0%	129%
$Ir(dF(CF_3)ppy)_2(dCF_3bpy)PF_6$	PCy_3	DCM	0%	7%	92%
$Ir(dF(CF_3)ppy)_2(dCF_3bpy)PF_6$	PCy_3	DME	1%	8%	108%

Catalyst	Ligand	Solvent	**4.31**	**4.32**	Remaining Alcohol
$Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$	KCN	DME	0%	0%	97%
$Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$	DMAP	DME	1%	1%	105%
$Ir(dF(CF_3)ppy)_2(dCF_3bpy)PF_6$	KCN	DME	0%	7%	100%
$Ir(dF(CF_3)ppy)_2(dCF_3bpy)PF_6$	DMAP	DME	1%	3%	101%

Table 4.29 Effects of ligands on the dual catalytic system

Tris(2,2′-bipyridine)ruthenium(II) hexafluorophosphate was also tested as a photocatalyst oxidant for Co(TAP) (Table 4.30). The same dual light source reactions were set up with ruthenium, testing the best conditions observed with iridium. A slight increase in conversion was observed, and little excess alcohol was formed. When cyanide was the ligand, **4.32** was the major product with dimer **4.33** a secondary product, and DMAP appears to favor dimer **4.33** slightly over **4.32**. These results are not overly surprising as without an H-donor we expect to see disproportionation and dimerization and with an oxidant, styrene should be formed preferentially over ethylbenzene. However, again we do not observe any consumption of 1-phenethylalcohol or product formation higher than 11%

total. These results are more encouraging than the iridium photocatalysts and should be studied further with H-donors and different ligands.



Ligand	Base	4.31	4.32	4.33	Remaining Alcohol
DMAP	–	0%	4%	7%	107%
KCN	–	1%	5%	4%	102%
KCN	$CsCO_3$	0%	8%	0%	104%
KCN	K_2CO_3	0%	5%	4%	105%

Table 4.30 $Ru(bpy)_3$ as photocatalyst for dual catalyst system

Ultimately, there are many shortcomings of this system that need to be investigated. The need for multiple light sources increases the reaction temperatures, even when using a fan, likely causing decomposition of complex **4.17**. Under the current reaction conditions, the photocatalysts appear to decrease conversion to the desired product and finally, still no turnover was observed.

4.12 Utilization of our Cobalt Photocatalyst for the Efficient Decomposition of Lignin into Useful Products

While striving to achieve turnover, we also investigated the possible utility of these cobalt-mediated reactions in other contexts. One such application is the ability to directly use hydroxyl groups in naturally-occurring polyols, reducing them into a host of useful products.[38–40] The direct activation of hydroxyl groups could be applied to compounds such as lignin, a major component of plant cell walls and an attractive polymeric feedstock

composed of methoxylated phenyl-propane units, which is challenging to degrade and utilize under current conditions.

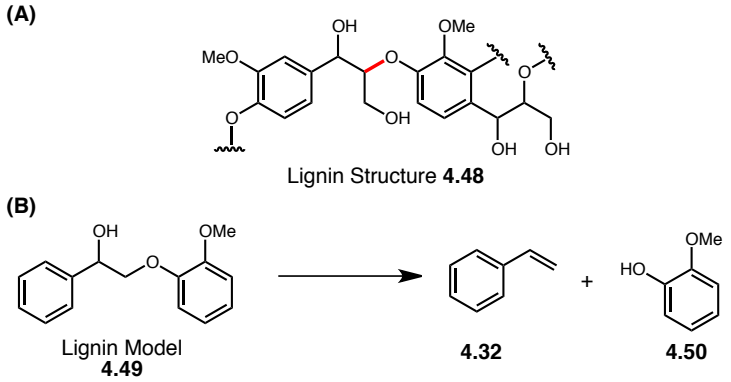


Figure 4.10 (A) lignin and (B) lignin model system

The major linkage between monolignol units, highlighted red in structure **4.48**,[41] would be the optimal position for cleavage (Figure 4.10, A). To study the feasibility of this we developed a model system **4.49** (Figure 4.10, B).[42] We envision the homolysis of the Co–C bond to initiate a radical decomposition cascade as outlined in Figure 4.11.

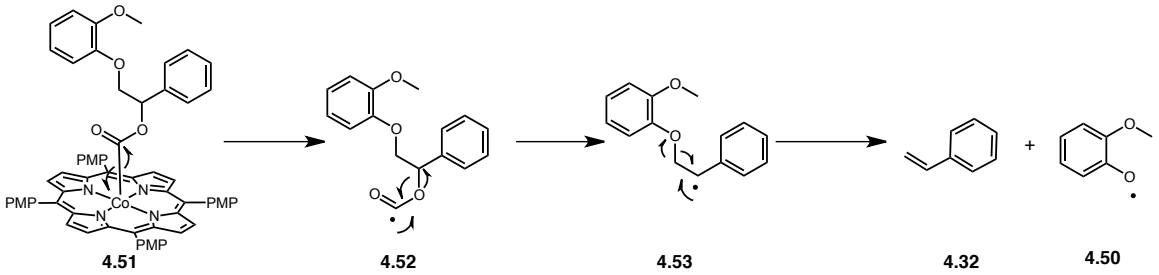
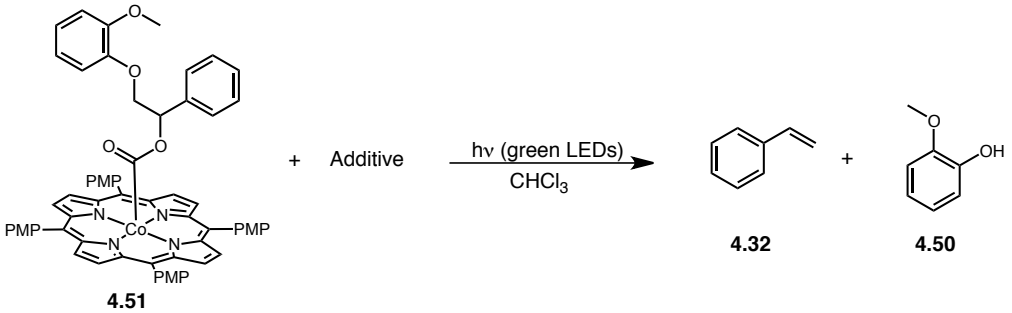


Figure 4.11 Proposed radical decomposition of lignin model **4.49**

After decarboxylation, the benzylic radical should promote the cleavage of the C–O bond to give styrene and the guaiacol radical. Finally, H-atom donation would give the desired methoxyphenol product. Initial studies are discussed in Chapter 3, and the best conditions were tested with the porphyrin ligand system (Table 4.31). In the absence of H-donor or ligand, minimal amounts of styrene were observed and no guaiacol was detected.

When benzimidazole was introduced as a ligand an increase in styrene was observed but again no product **4.50** was observed. Once an H-donor was introduced, styrene yield increased and guaiacol was finally observed, although not to the quantity expected. The first detection of guaiacol and increase in styrene with an H-donor makes sense as previously there was no termination step and the guaiacol radical likely reacted with benzylic radical **4.53** or recombined with styrene. Finally, the combination of triisopropylthiophenol and Hantzsch ester was tested and interestingly formed ethylbenzene as the sole product in 17% yield. Although surprising, previous control studies indicated that under these reaction conditions styrene can be consumed to make ethylbenzene, but the loss of product **4.50** remains unexplained. Overall, although styrene was observed and a small amount of guaiacol was detected, the fate of the remaining fragment is still unknown. This initial look into applications of our methodology show promise with the need for further study.



Additive	Ethylbenzene	Styrene	Methoxyphenol
–	0%	9%	0%
Benzimidazole	0%	35%	0%
Triisopropylthiophenol	0%	52%	15%
Triisopropylthiophenol/Hantzsch	17%	0%	0%

Table 4.31 Additive test for the radical decomposition of **4.51**

4.12 Conclusions

We have described a method for *in-situ* oxidation-carbonylation methods utilizing porphyrin ligands of varying electronics. Diverse alcohols undergo efficient carbonylation with Co-porphyrins to produce alkoxycarbonyl cobalt species with as low as 1 atm of carbon monoxide. Irradiation of these alkoxycarbonyl complexes causes the homolysis of our desired Co–C bond and trapping of the decarboxylated alkyl radicals with TEMPO was achieved. Irradiation under specific ligand and H-donor combinations can give targeted selectivity to achieve either the reduced or eliminated product in high yields. This strategic approach enables the C–O bond activation of alcohols and alkyl radical generation with carbon dioxide as the only byproduct and establishes the fundamental processes for a cobalt-mediated C–O bond activation strategy.

Efforts to extend this carbonylation-homolysis-decarboxylation process to a catalytic method are currently facing complications. However catalytic conditions under a dual catalytic system show promise. Applications for the direct activation of hydroxyl groups in lignin using our model system have shown some interesting progress but require further investigation into the fate of the guaiacol product.

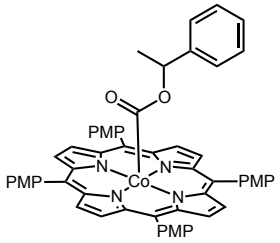
4.13 Experimental

All reactions were carried out in oven dried or flame dried glassware charged with a magnetic stir bar, were prepared under inert nitrogen atmosphere, and subsequently degassed with carbon monoxide. Solvents were dried by passage through alumina columns. Commercially available alcohols were distilled from calcium hydride prior to use. Co(II)

Porphyrins were prepared according to known literature procedures or purchased and used as received.[10,11,14,43]

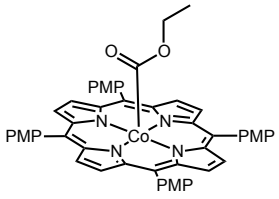
Procedure A: To a mixture of Co(II) Porphyrin and DDQ was added 21 mL toluene and the respective alcohol. The reaction mixture was degassed and pressurized to 7.0 atm CO using a Parr pressure vessel and stirred for the indicated time, in the dark, at room temperature. Upon completion solvent was removed and the crude reaction mixture was recrystallized from CH_2Cl_2 and heptane. The red precipitate was filtered through Celite and washed several times with heptane remove excess unreacted alcohol. Subsequent washing with 2:1 Hexanes: CH_2Cl_2 separated the product from remaining Co(II) starting material. The red Co(III) filtrate was concentrated to yield a red solid. No further purification was required.

Procedure B*:* To a mixture of alkoxycarbonyl cobalt(II) porphyrin and TEMPO was added 1.5 mL of $CHCl_3$ and the reaction mixture was degassed by three cycles of freeze-pump-thaw. The reaction mixture was stirred for 4 h at room temperature and irradiated by 450/550 nm LEDs. Upon completion, the Co(II) product was precipitated by addition of heptane. Filtration through Celite washing several times with heptane separated the TEMPO-trapped product and subsequent washing with CH_2Cl_2 isolated the Co(II) porphyrin. Concentration of the filtrates gave desired products with no further purification required.



1-phenethyloxycarbonyl-cobalt meso-(4-methoxy-phenyl) Porphyrin (4.17)

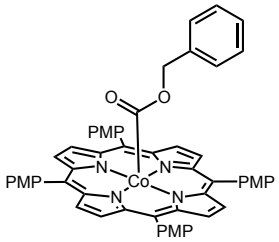
Prepared according to the general procedure A using 190 mg Cobalt meso-(4-methoxy-phenyl) porphyrin (0.25 mmol, 1.0 equiv), 150 μL 1-phenylethanol (1.25 mmol, 5.0 equiv) and 57 mg DDQ (0.25 mmol, 1.0 equiv). After 16 h, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (220 mg, 0.23 mmol, 92%). IR (film) 2957, 2833, 1690, 1504, 1241, 996 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 8H), 7.90 (s, br, 8H), 7.33 (d, *J* = 8.8 Hz, 8H), 6.85 (t, *J* = 7.4 Hz, 1H), 6.70 (t, *J* = 7.7 Hz, 2H), 4.95 (d, *J* = 7.3 Hz, 2H), 4.03 (d, *J* = 8.0 Hz, 12H), 2.90 (q, *J* = 6.2 Hz, 1H), -0.75 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.8, 143.8, 143.7, 141.5, 134.5, 133.9, 132.1, 127.1, 126.1, 123.2, 119.0, 112.4, 69.2, 55.4, 21.3; HRMS (ESI) *m / z* calcd for $C_{57}H_{45}CoN_4O_6Na$ $(M + Na)^+$ 963.2563, found 963.2533.



Ethoxycarbonyl-cobalt meso-(4-methoxy-phenyl) Porphyrin (4.18)

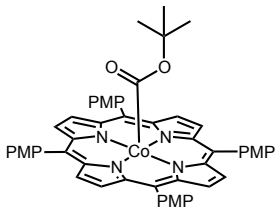
Prepared according to the general procedure A using 190 mg cobalt meso-(4-methoxy-phenyl) porphyrin (0.25 mmol, 1.0 equiv), 73 μL ethanol (1.25 mmol, 5.0 equiv) and 57 mg DDQ (0.25 mmol, 1.0 equiv). After 16 h, the reaction mixture was worked up

as outlined in the general procedure. Reaction afforded a red crystalline solid (190 mg, 0.22 mmol, 87%). IR (film) 2931, 1691, 1570, 1287, 1001 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 8H), 8.04 (d, *J* = 8.0 Hz, 8H), 7.25 (d, *J* = 8.4 Hz, 8H), 4.07 (s, 12H), 1.64 (q, *J* = 7.0 Hz, 2H), -0.74 (t, *J* = 7.0 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 145.9, 134.8, 134.3, 132.7, 121.8, 112.48, 62.67, 55.68, 13.01.; HRMS (ESI) *m / z* calcd for $C_{51}H_{42}CoN_4O_6$ $(M+ H)^+$ 865.2431, found 865.2453.



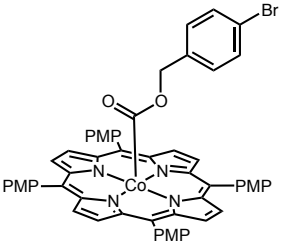
Benzyloxycarbonyl-cobalt meso-(4-methoxy-phenyl) Porphyrin (4.19)

Prepared according to the general procedure A using 190 mg cobalt meso-(4-methoxy-phenyl) porphyrin (0.25 mmol, 1.0 equiv), 130 μL benzyl alcohol (1.25 mmol, 5.0 equiv) and 57 mg DDQ (0.25 mmol, 1.0 equiv). After 16 h, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (215 mg, 0.23 mmol, 93%). IR (film) 2933, 1688, 1606, 1246, 1025 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 8H), 7.92 (s, br, 8H), 7.24 (d, *J* = 8.0 Hz, 10H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.86 (t, *J* = 7.5 Hz, 2H), 5.34 (d, *J* = 7.5 Hz, 2H), 4.07 (s, 12H), 2.63 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 145.9, 134.7, 134.3, 132.7, 127.8, 127.2, 126.3, 1.8, 112.4, 67.9, 55.7; HRMS (ESI) *m / z* calcd for $C_{56}H_{43}CoN_4O_6$ M^+ 926.2509, found 926.252



***tert*-butyloxycarbonyl-cobalt meso-(4-methoxy-phenyl) Porphyrin (4.20)**

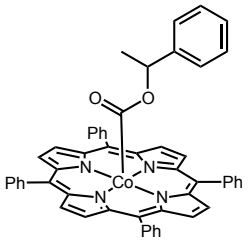
Prepared according to the general procedure A using 190 mg cobalt meso-(4-methoxy-phenyl) porphyrin (0.25 mmol, 1.0 equiv), 120 μL *tert*-butyl alcohol (1.25 mmol, 5 equiv) and 57 mg DDQ (0.25 mmol, 1.0 equiv). After 16 h, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (130 mg, 0.15 mmol, 60%). IR (film) 2928, 1692, 1507, 1247, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.88 (s, 8H), 8.03 (s, 8H), 7.25 (d, J = 8.8 Hz, 8H), 4.07 (s, 12H), -0.75 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 145.6, 134.7, 134.4, 132.5, 121.0, 112.3, 55.6, 25.8; HRMS (ESI) *m / z* calcd for $C_{53}H_{45}CoN_4NaO_6Na$ $(M + Na)^+$ 915.2569, found 915.2567.



4-bromobenzyloxycarbonyl-cobalt meso-(4-methoxy-phenyl) Porphyrin (4.21)

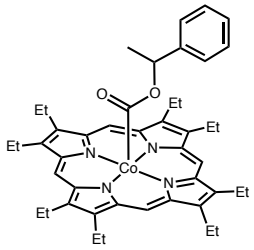
Prepared according to the general procedure A using 190 mg cobalt meso-(4-methoxy-phenyl) porphyrin (0.25 mmol, 1.0 equiv), 230 mg 4-bromobenzylalcohol (1.25 mmol, 5.0 equiv) and 57 mg DDQ (0.25 mmol, 1 equiv). After 16 h, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (230 mg, 0.23 mmol, 94%). IR (film) 2954, 1671, 1607, 1247, 1001 cm^{-1}; ^1H NMR

(400 MHz, $CDCl_3$) δ 8.89 (s, 8H), 7.89 (s, br, 8H), 7.23 (d, *J* = 8.8 Hz, 8H), 6.97 (d, *J* = 8.2 Hz, 2H), 5.19 (d, *J* = 8.2 Hz, 2H), 4.07 (s, 12H), 2.53 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 145.8, 134.7, 134.4, 134.1, 132.8, 130.9, 128.3, 121.8, 112.5, 67.0, 55.7; HRMS (ESI) *m / z* calcd for $C_{56}H_{42}BrCoN_4ONa^+$ 1027.1512, found 1027.1534.



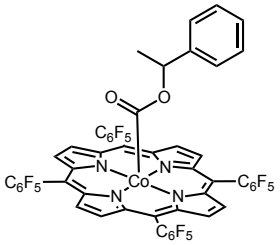
1-phenethyloxycarbonyl-cobalt meso-(tetraphenyl) Porphyrin (4.22)

Prepared according to the general procedure A using 170 mg cobalt tetraphenyl porphyrin (0.25 mmol, 1.0 equiv), 150 μL 1-phenylethanol (1.25 mmol, 5.0 equiv) and 57 mg DDQ (0.25 mmol, 1.0 equiv). After 16 h, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (230 mg, 0.23 mmol, 94%). IR (film) 3055, 2925, 1693, 1599, 1351, 1003 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 8H), 8.00 (s, br, 8H), 7.79 – 7.74 (m, 12H), 6.85 (t, *J* = 7.4 Hz, 1H), 6.70 (t, *J* = 7.7 Hz, 2H), 4.97 (d, *J* = 7.2 Hz, 2H), 2.92 (q, *J* = 6.5 Hz, 1H), -0.73 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.5, 143.4, 141.6, 133.5, 132.2, 127.7, 127.1, 126.9, 126.1, 123.2, 119.4, 69.4, 21.2; HRMS (ESI) *m / z* calcd for $C_{53}H_{37}CoN_4O_6Na^+$ 843.2141, found 843.2127.



1-phenethyloxycarbonyl-cobalt octaethylporphyrin (4.23)

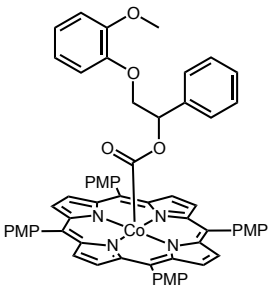
Prepared according to the general procedure A using 59 mg cobalt octaethylporphyrin (0.10 mmol, 1.0 equiv), 24 μL 1-phenylethanol (0.20 mmol, 2.0 equiv) and 23 mg DDQ (0.1 mmol, 1 equiv). After 16 h, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (62 mg, 0.08 mmol, 84%). IR (film) 2964, 2870, 1697, 1263, 1021 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 4H), 6.79 (t, *J* = 7.4 Hz, 1H), 6.67 (t, *J* = 7.6 Hz, 2H), 4.96 (d, *J* = 7.4 Hz, 2H), 4.17 – 3.97 (m, 16H), 2.96 (q, *J* = 6.4 Hz, 1H), 1.93 (dd, *J* = 12.7, 7.4 Hz, 24H), -0.82 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 142.9, 143.1, 141.1, 127.1, 126.2, 123.6, 99.3, 72.3, 20.9, 20.1, 18.6.; HRMS (ESI) *m / z* calcd for $C_{45}H_{53}CoN_4O_2Na$ $(M + Na)^+$ 763.3393, found 763.3426.



1-phenethyloxycarbonyl-cobalt tetrakis(pentafluorophenyl)porphyrin (4.24)

Prepared according to the general procedure A using 260 mg cobalt meso-Tetrakis(pentafluorophenyl)porphyrin (0.25 mmol, 1.0 equiv), 53 μL 1-phenylethanol (0.50 mmol, 2.0 equiv) and 57 mg DDQ (0.25 mmol, 1.0 equiv). After 16 h, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red

crystalline solid (170 mg, 0.14 mmol, 56%). IR (film) 2928, 1648, 1476 1217, 1007 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (d, *J* = 7.3 Hz, 8H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.63 (t, *J* = 7.6 Hz, 2H), 5.05 (d, *J* = 7.7 Hz, 2H), 3.22 (q, *J* = 6.5 Hz, 1H), -0.57 (d, *J* = 6.5 Hz, 3H). ^{19}F NMR (400 MHz, $CDCl_3$) δ -133.93, -137.47, -151.50.; HRMS (ESI) *m / z* calcd for $C_{53}H_{17}CoN_4O_2F_{20}$ Na $(M)^+$ 1180.0364, found 1180.0408.



Alkoxycarbonyl-cobalt porphyrin (4.51)

Prepared according to the general procedure A using 79 mg cobalt meso-(4-methoxy-phenyl) porphyrin (0.10 mmol, 1.0 equiv), 50 mg 2-(2-methoxyphenoxy)-1-phenylethanol (0.20 mmol, 2.0 equiv) and 23 mg DDQ (0.10 mmol, 1.0 equiv). After 16 h, the reaction mixture was worked up as outlined in the general procedure. Reaction afforded a red crystalline solid (70 mg, 0.07 mmol, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 8H), 7.98 (s, 8H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 8H), 6.93 (q, *J* = 7.5 Hz, 1H), 6.86 (t, *J* = 7.6 Hz, 1H), 6.81 – 6.75 (m, 1H), 6.70 (t, *J* = 7.6 Hz, 2H), 6.66 – 6.55 (m, 2H), 5.72 (dd, *J* = 8.0, 1.5 Hz, 1H), 5.08 (d, *J* = 7.7 Hz, 2H), 3.41 (s, 3H).

4.14 References

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Chapter 5 : Progress Towards the Synthesis of Fraxinellonone

5.1 Introduction

The limonoid family of natural products exhibit significant neuroprotective effects against glutamate toxicity, which is implicated in models of three important neurodegenerative diseases.[2] Despite their challenging architecture and wide spectrum of biological activities, the limonoids have attracted only limited attention from synthetic organic chemists, and a general strategy for the synthesis of the vast majority of the family has not been reported.[3]

Recently, in an investigation of plants used in traditional Korean medicine, Kim and co-workers reported that treatment of rat cortical cells with 50 nM of limonoid natural products resulted in a 30–57% improvement in cell survival against glutamate toxicity.[6] Further evaluation of the structural requirements for activity, in particular variations to the conserved furan substituent that are not available biosynthetically, will require the synthesis of unnatural analogs. The development of a general route for the synthesis of fraxinellonone and analogs, which will also be amenable to the synthesis of more complex members of the limonoid family is of interest.

5.2 Previous Synthesis Methods

The structure of fraxinellonone was first elucidated in 1990 by Bon and coworkers[1] which was significantly later than fraxinellone, which was first isolated in 1965.[2] The first

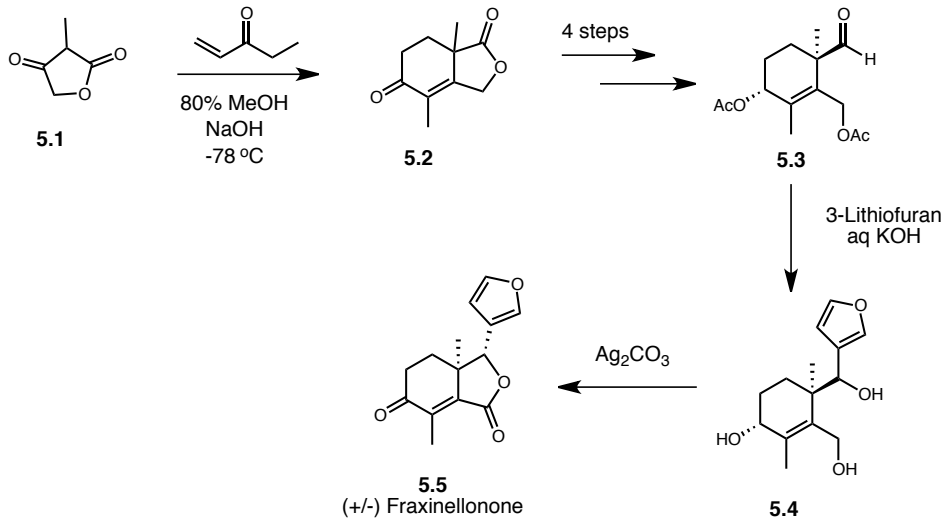


Figure 5.1 First reported synthesis of (+/-) fraxinellonone

synthesis of fraxinellonone was reported by Nakatani and coworkers in 1997[3] with a 7-step synthesis to make a racemic mixture (Figure 5.1). Although fraxinellonone was synthesized this synthetic pathway leaves much to be desired. After forming compound **5.2**, four steps are required to cleave the lactone and protect the alcohols in order to introduce the furan ring in compound **5.4**. Finally, with the use of silver carbonate, lactonization and oxidation is achieved for the formation of fraxinellonone **5.5**.

A later synthesis (in 2005) by Morken and coworkers utilized an stereoselective Oshima–Utimoto reaction to form isofraxinellone in 7 steps (Figure 5.3).[4] Oxidation of isofraxinellone **5.7** gave epoxide **5.8** and its diastereomer in a 1:1.6 ratio favoring epoxide **5.8**. Treatment of epoxide **5.8** with DBU introduces the desired unsaturation in compound **5.9**. Finally, oxidation of **5.9** to the desired fraxinellonone product **5.5** was achieved. Although this method utilized some interesting selective chemistry, it was ultimately not an efficient way to synthesize **5.5**.

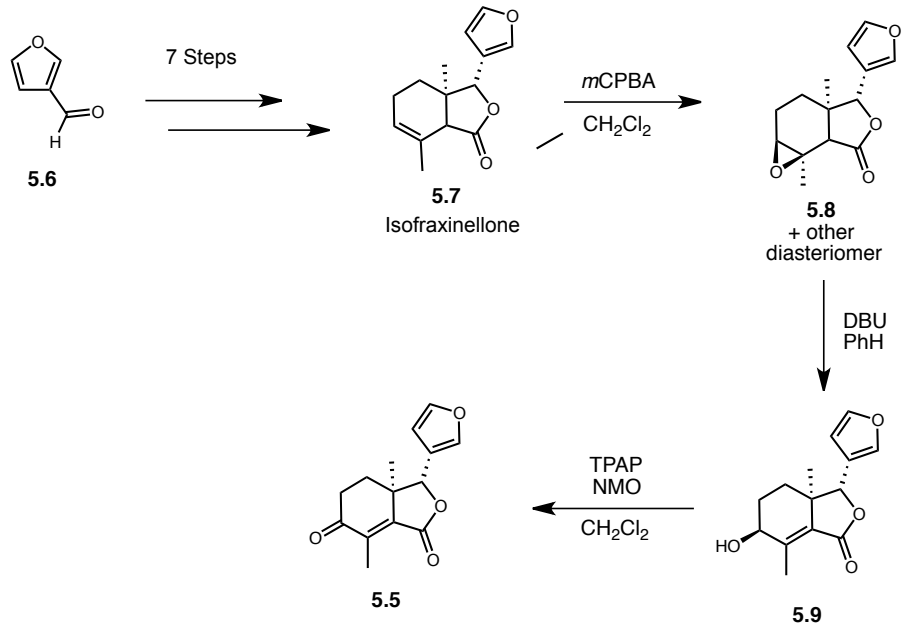


Figure 5.3 Morken's synthesis of fraxinellonone

Finally, in 2012, Xu and coworkers selectively oxidized fraxinellone **5.10** with CrO_3, pyridine and *tert*-butyl hydrogenperoxide to give fraxinellonone **5.5** in modest yields (Figure 5.2).[5] This method is convenient as it provides a direct, selective method for derivatization of fraxinellone, however, has not addressed issues of enantioselectivity or decreased the steps it takes to synthesize these degraded limonoids.

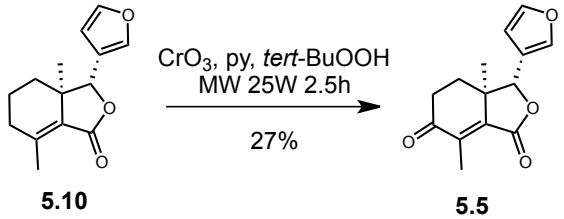


Figure 5.2 Oxidation of fraxinellone **5.10** to fraxinellonone **5.5**

5.3 Progress Towards the Synthesis of Fraxinellonone

We propose a short (5 step) synthesis to fraxinellonone that utilizes our developed cobalt photocatalyst (Figure 5.4). Fraxinellonone **5.5** is formed by a carbonylation-

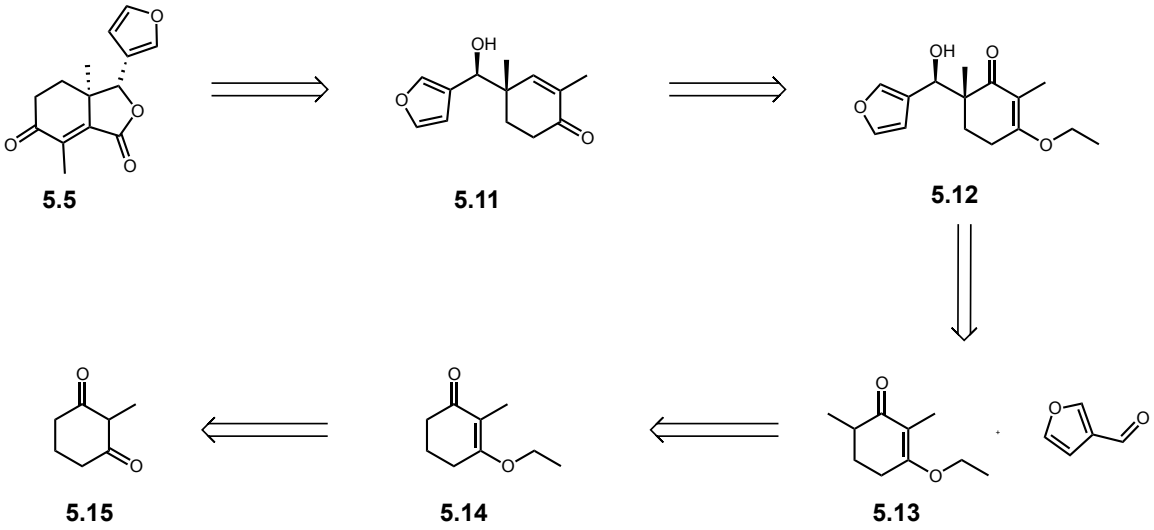


Figure 5.4 Retrosynthetic strategy for the synthesis of fraxinellonone

lactonization reaction using our cobalt photocatalyst from alcohol **5.11**. Alcohol **5.11** is synthesized through a Stork-Danheiser transposition of vinylogous ester **5.12**. An aldol reaction between vinylogous ester **5.13** and furfural would produce product **5.12**. Vinylogous ester **5.13** would be formed by methylation of **5.14** which is formed from 2-methylcyclohexane-1,3-dione (**5.15**).

The synthesis of keto ether **5.14** was achieved in great yields (67% yield) using ethanol, tosic acid and a Dean-Stark apparatus for the removal of water (Figure 5.5).[6] This

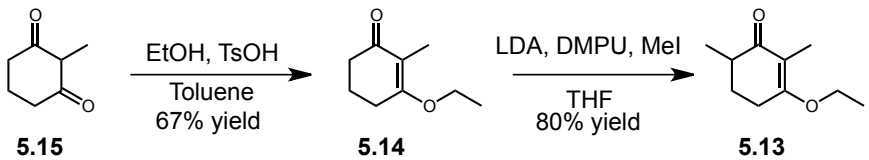


Figure 5.5 Synthesis of vinylogous ester **5.13**

reaction could be performed on a multigram scale without loss in yield. Methylation of **5.14** to vinylogous ester **5.13** was accomplished by addition of methyliodide to the enolate formed when **5.14** was added to a solution of LDA.[7] Addition of 0.8 equiv DMPU to the reaction mixture increased the yield of **5.13**, although, the reaction will still proceed sufficiently without DMPU (70% yield vs 80% yield). Again, this reaction could be run on a multigram scale without sacrificing high yields. The aldol condensation reaction between vinylogous ester **5.13** and 3-furaldehyde has not previously been studied (Figure 5.6).

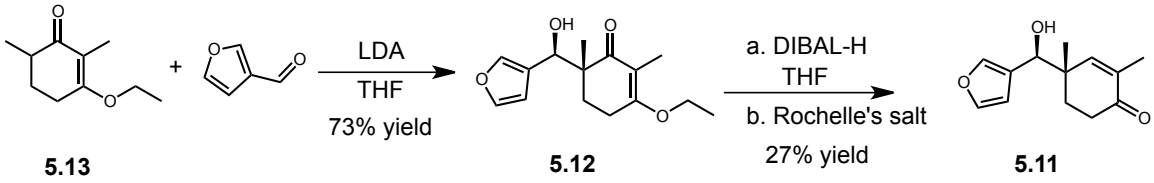


Figure 5.6 Aldol reaction and Stork-Danheiser transposition

Hernandez and coworkers have achieved a similar condensation between 2,6-dimethylcyclohexanone and furfural which we have used as our conditions.[8] The conversion to aldol product **5.12** is high (73% yield) although is significantly slower than the hexanone precedent (>1 h vs 20 min). Additionally, this reaction is extremely sensitive

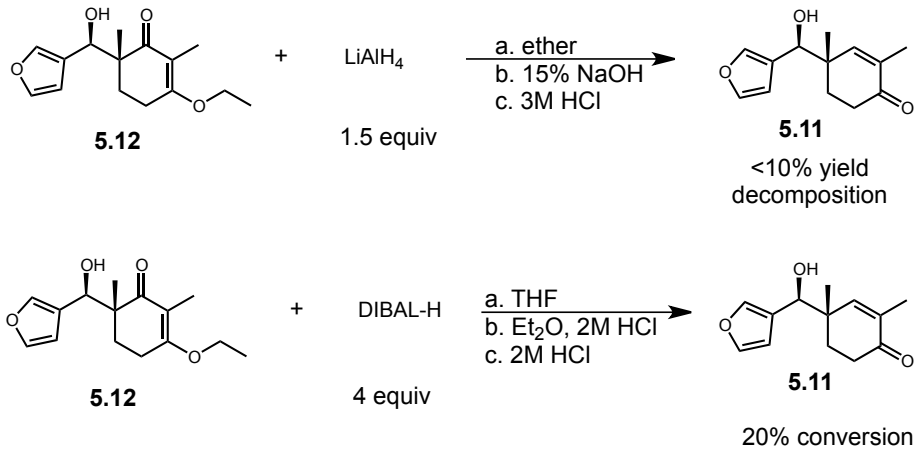
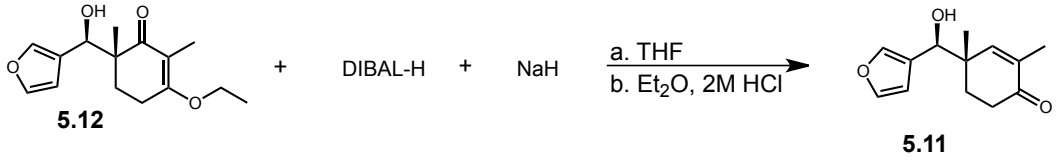


Figure 5.7 Study of hydride sources for reduction of **5.12**

to the condition of 3-furaldehyde which must be distilled while the enolate of **5.13** is forming. Allowing 3-furaldehyde to sit after distillation results in a drastic decrease in product formation. The aldol reaction under these reaction conditions gives a single diastereomeric product and chemical shift data, both ^{1}H and ^{13}C NMR, compared similar compounds suggests we have formed diastereomer **5.12**.[8,9] Next, reduction of vinylogous ester **5.12** with DIBAL-H and aqueous workup with Rochelle's salt resulted in the Stork-Danheiser transposition product **5.11**. Although modest yields were obtained, the combination of DIBAL and Rochelle's salt gave the optimal yields. Initial studies of the reduction included examinations into hydride sources and workup conditions (Figure 5.7). The use of $LiAlH_4$ (1.5 equiv) was consistently met with low conversion to **5.11** and decomposition of **5.12**.[10] When examining DIBAL-H, conversion was still low but retention of starting material **5.12** was high. One consideration of these reactions is the secondary alcohol. An excess of DIBAL-H is required to first deprotonate the alcohol and then reduce the carbonyl. This excess can be causing decomposition, so an auxiliary deprotonating agent was examined (Table 5.1). Using sodium hydride to deprotonate the



Equiv DIBAL	**5.11**
1	7%
2	16%
4	21%

Table 5.1 Examination of equivalents of DIBAL and NaH in the reduction of **5.12**

alcohol, a screen of DIBAL equivalents demonstrated that even when deprotonated, compound **5.12** requires at least 2 equivalents of reducing agents.

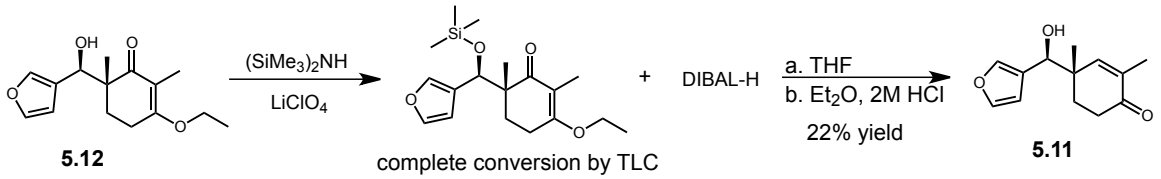
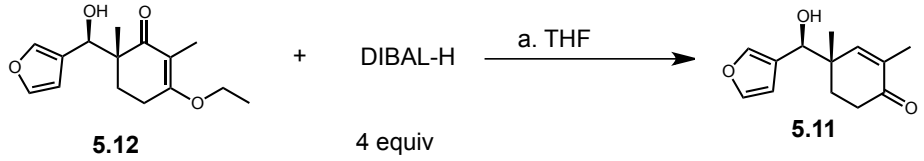


Figure 5.8 Protection of **5.12** and reduction with DIBAL

Alternatively, we protected the pseudo-benzylic alcohol with a trimethylsilyl protecting group (Figure 5.8).[11] When the protection of the secondary alcohol went to completion by TLC, 2 equivalents of DIBAL were added to the reaction. Although there is a slight increase in yield, most of the vinylogous ester is not being reduced. Finally, the aqueous workup conditions were tested (Table 5.2). A Fieser workup to remove aluminum salts was found to be ineffective. Additionally, when acid was employed in the workup a decomposition of both **5.12** and **5.11** was observed. The best workup conditions were found to be an aqueous workup using Rochelle's Salt. Optimization for the Stork-Danheiser transposition is still necessary for this reaction.



Work-up	Washes	**5.12**	**5.11**
Rochelle's Salt	H_2O	37%	15%
Rochelle's Salt	HCl	32%	9%
Fieser	HCl	–	–

Table 5.2 Investigation of aqueous workup conditions

5.4 Lactonization using our Cobalt Photocatalyst

Lactonization reactions were examined using alcohol **5.11** in the presence of Co(TAP), Co(OEP) and $Co_2(CO)_8$. These one-pot catalytic reactions did not give promising results, so we examined the stepwise carbonylation-lactonization reaction (Figure 5.9). Carbonylation of **5.11** was highly efficient (90% yield) and gave pure product after recrystallization. Unfortunately, irradiation of carbonylated product **5.16** did not give any desired product **5.5**. Additional investigations into this lactonization reaction are required.

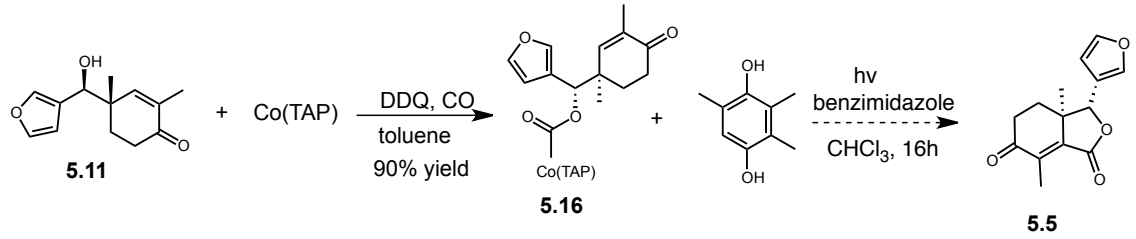


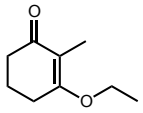
Figure 5.9 Stepwise carbonylation-irradiation to form fraxinellonone

5.5 Conclusions

The progress towards the shortest synthesis of fraxinellonone using a cobalt photocatalyst has been demonstrated. Optimization conditions for a Stork-Danheiser transposition are still required as well as the final lactonization protocol. Likely, a model system should be utilized to improve the final cyclization so it can be implemented with fraxinellonone. The ability to access this degraded limonoid is both an interesting application for the cobalt methodology and useful for the structure-function studies of their biological activities.

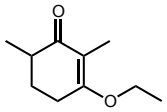
5.6 Experimental

All reactions were carried out in oven dried or flame dried glassware charged with a magnetic stir bar, were prepared under inert nitrogen atmosphere, and subsequently degassed with carbon monoxide. Solvents were dried by passage through columns of activated alumina. Anhydrous dichloroethane (DCE) was dried over 5 Å sieves to remove trace amounts of methanol. Commercially available alcohols were distilled from calcium hydride prior to use.



3-ethoxy-2-methylcyclohex-2-enone (5.14)

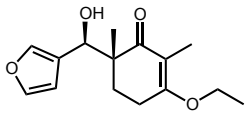
To 3.0 g 2-methyl-1,3-cylohexanedione (23 mmol, 1.0 equiv) and 92 mg *p*-toluenesulfonic acid (0.50 mmol, 0.02 equiv) was added 56 mL toluene and 30 mL ethanol. The reaction mixture was heated to reflux with a Dean-Stark apparatus and was stirred overnight. Upon completion, reaction mixture was concentrated and purified by silica gel column chromotrography (40% EtOAc in Hexanes). Reaction afforded a clear oil (2.4 g, 15 mmol, 67%). Product consistent with literature values.[6]



3-ethoxy-2,6-dimethylcyclohex-2-enone (5.13)

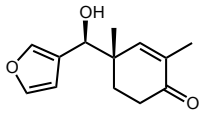
To a solution of 2.1 mL diisopropylamine (1.36 mmol, 1.15 equiv) and 13 mL THF at 0 ºC was added 9.3 mL *n*-butyllithium (1.6 M in hexanes). After 15 min, the reaction mixture was cooled to -78 ºC and 2.0 g **5.14** (13 mmol, 1.0 equiv) in a 7.0 mL solution of THF was added. The reaction mixture was stirred for 1 h then 1.3 mL DMPU (11 mmol,

0.80 equiv) and 0.90 mL of methyl iodide in a 3.0 mL solution of THF was added. The reaction was stirred for an additional 2 h at -78 ºC then was warmed to rt over 1 h and stirred at rt overnight. Upon completion, reaction mixture was poured into water, extracted with ether, washed with water and brine, and dried with sodium sulfate. Purification by silica gel chromatography (40% EtOAc in hexanes) afforded a yellow oil (2.2 g, 10. mmol, 80% yield). Product consistent with literature values.[7]



(*R*)-3-ethoxy-6-((*R*)-furan-3-yl(hydroxy)methyl)-2,6-dimethylcyclohex-2-enone (5.12)

To a solution of 0.3 mL diisopropylamine (0.20 mmol, 1.1 equiv) and 6.0 mL THF at 0 ºC was added 1.4 mL *n*-butyllithium (1.6 M in hexanes). After 15 minutes, the reaction mixture was cooled to -78 ºC and 340 mg **5.13** was added dropwise. The reaction mixture stirred for 25 min then 0.18 mL freshly distilled furfural (2.0 mmol, 1.0 equiv) was added rapidly. The reaction was stirred for 1h at -78 ºC then was quenched with saturated NH_4Cl and warmed to rt over 30 min. Extraction with ether and purification with silica gel chromatography (20% EtOAc in hexanes) gave a yellow oil (410 mg, 1.6 mmol, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 7.6 Hz, 2H), 6.38 (d, J = 1.9 Hz, 1H), 5.39 (s, 1H), 4.82 (s, 1H), 4.09 (q, J = 7.2 Hz, 1H), 4.05 (q, J = 7.2 Hz, 1H), 2.61 – 2.41 (m, 2H), 1.70 (s, 4H), 1.49 (ddd, J = 13.3, 5.1, 3.2 Hz, 1H), 1.36 (t, J = 7.0 Hz, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.2, 171.6, 142.5, 140.7, 124.25, 112.9, 110.4, 72.2, 63.7, 45.1, 29.9, 22.0, 15.3, 14.9, 7.7; HRMS (ESI) *m / z* calcd for $C_{15}H_{21}O_4$ $(M + H)^+$ 265.1440, found 265.1438.



(*R*)-4-((*R*)-furan-3-yl(hydroxy)methyl)-2,4-dimethylcyclohex-2-enone (5.11)

To 52 mg **5.12** (0.20 mmol, 1.0 equiv) in 2.5 mL toluene at -78 ºC was added 0.80 mL (4.0 equiv) DIBAL-H (1M in THF). The reaction mixture was stirred for 1 h at -78 ºC, then diluted with 2.0 mL Et_2O and quenched with sat. aq. Rochelle's salt. Extraction with Et_2O and washing with water and Rochelle's salt solution, and purification with silica gel chromatography (10% DCM, 20% EtOAc in hexanes) afforded a white amorphous solid (11 mg, 0.05 mmol, 27% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 1.4 Hz, 2H), 6.73 (s, 1H), 6.38 (s, 1H), 4.61 (s, 1H), 2.56 – 2.40 (m, 2H), 2.06 – 1.92 (m, 1H), 1.78 (s, 3H), 1.67 (m, 2H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.8, 150.7, 143.2, 140.29, 134.8, 125.0, 109.8, 73.9, 34.2, 31.6, 20.3, 16.5; HRMS (ESI) m / z calcd for $C_{13}H_{16}O_3$ $(M)^+$ 220.1099, found 220.1111.

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